JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1964

PROBLEMS OUTSTANDING IN THE
EVOLUTION OF BRAIN FUNCTION

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Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934

C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races;* April 25, 1935

Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders;* May 15, 1936

R. W. Gerard, *Dynamic Neural Patterns;* April 15, 1937

Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull;* May 5, 1938

G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates;* May 11, 1939

John F. Fulton, *A Functional Approach to the Evolution of the Primate Brain;* May 2, 1940

Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates;* May 8, 1941

George Pinkley, *A History of the Human Brain;* May 14, 1942

James W. Papez, *Ancient Landmarks of the Human Brain and Their Origin;* May 27, 1943

James Howard McGregor, *The Brain of Primates;* May 11, 1944

K. S. Lashley, *Neural Correlates of Intellect;* April 30, 1945

Warren S. McCulloch, *Finality and Form in Nervous Activity;* May 2, 1946

S. R. Detwiler, *Structure-Function Correlations in the Developing Nervous System as Studied by Experimental Methods;* May 8, 1947

Tilly Edinger, *The Evolution of the Brain;* May 20, 1948

Donald O. Hebb, *Evolution of Thought and Emotion;* April 20, 1949

Ward Campbell Halstead, *Brain and Intelligence;* April 26, 1950

Harry F. Harlow, *The Brain and Learned Behavior;* May 10, 1951

Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex;* May 7, 1952

Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History;* May 21, 1953

Horace W. Magoun, *Regulatory Functions of the Brain Stem;* May 5, 1954

Fred A. Mettler, *Culture and the Structural Evolution of the Neural System;* April 21, 1955

Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny;* April 26, 1956

Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man;* April 25, 1957

David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action;* May 8, 1958

Charles R. Noback, *The Heritage of the Human Brain;* May 6, 1959

Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization;* May 26, 1960

Paul I. Yakovlev, *Brain, Body and Behavior. Stereodynamic Organization of the Brain and of the Motility-Experience in Man Envisaged as a Biological Action System;* May 16, 1961

H. K. Hartline, *Principles of Neural Interaction in the Retina;* May 29, 1962

Harry Grundfest, *Specialization and Evolution of Bioelectric Activity;* May 28, 1963

Roger W. Sperry, *Problems Outstanding in the Evolution of Brain Function;* June 3, 1964

PROBLEMS OUTSTANDING IN THE EVOLUTION OF BRAIN FUNCTION

Having been for some time one of those "card-carrying members" of the American Museum and being indebted to the Museum on certain other counts over the years, I much appreciate the invitation to give the 1964 James Arthur Lecture. I have been forewarned that many in the audience will not be particularly carried away by the "latest technical advances." I have also been forewarned that another 50 per cent are apt to be rather bored by anything else. The motley mixture of material with which I have tried to balance the diverse interests will, I fear, strain even so broad an encompassing theme as that of evolution. As indicated in the title, we shall be concerned more with the functional than with the morphological properties of the brain, and more with remaining unsolved problems than with the solid progress over which we already can beat our chests.

I wish to skip the beginning steps in the evolution of the human brain and pick up the story at about the culmination of the latter half of the age of hydrogen gas. In such a way we can bypass what is by far the most difficult of all the unsolved problems in brain evolution, namely, how, when, and where did the hydrogen age and the whole business start? This problem we can leave to the proponents of the "steady state," the "periodic pulsation," and the "big bang," at least until someone comes along with a more credible interpretation of the meaning of the red shift.

We can skip quickly also through those early periods when, first, electrons and protons were being used to build bigger and better atoms, and then the atoms to make bigger and finer molecules, and then these in turn were being compounded into giant and replicating molecules and self-

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organizing molecular complexes and eventually that elaborate unit, the living cell.

We need pause here only to note for future reference that evolution keeps complicating the universe by adding new phenomena that have new properties and new forces and that are regulated by new scientific principles and new scientific laws—all for future scientists in their respective disciplines to discover and formulate. Note also that the old simple laws and primeval forces of the hydrogen age never get lost or cancelled in the process of compounding the compounds. They do, however, get superseded, overwhelmed, and outclassed by the higher-level forces as these successively appear at the atomic, the molecular, and the cellular and higher levels.

We can turn now to what is probably the "most unanswered" problem in brain evolution. We encounter it a bit later on, presumably after organisms with nerve nets and brains have entered the picture. I refer, as you probably guess, to the first appearance of that most important of all brain properties and certainly the most precious, conscious awareness. (I hope that it is safe to assume that, since "mind" and "consciousness" have made a comeback in recent years and have become respectable terms again in the Boston area, it is permissible to mention them here also.)

In any case, the fossil record notwithstanding, there seems to be good reason to regard the evolutionary debut of consciousness as very possibly the most critical step in the whole of evolution. Before this, the entire cosmic process, we are told, was only, as someone has phrased it, "a play before empty benches"—colorless and silent at that, because, according to our best physics, before brains there was no color and no sound in the universe, nor was there any flavor or aroma and probably rather little sense and no feeling or emotion.

All of these can now be generated by the surgeon's elec-

trode tip applied to the proper region of the exposed conscious brain. They can be triggered also, of course, by the proper external stimuli, but also, more interestingly, by centrally initiated dream states, illusionogenic and hallucinogenic agents, but always and only within and by a brain. There probably is no more important quest in all science than the attempt to understand those very particular events in evolution by which brains worked out that special trick that has enabled them to add to the cosmic scheme of things: color, sound, pain, pleasure, and all the other facets of mental experience.

In searching brains for clues to the critical features that might be responsible, I have never myself been inclined to focus on the electrons, protons, or neutrons of the brain, or on its atoms. And, with all due respect to biochemistry and the N.R.P., I have not been inclined to look particularly at the little molecules of the brain or even at its big macromolecules in this connection. It has always seemed rather improbable that even a whole brain cell has what it takes to sense, to perceive, to feel, or to think on its own. The "search for psyche," in our own case at least, has been directed mainly at higher-level configurations of the brain, such as specialized circuit systems, and not just any juicy central nerve network that happens to be complex and teeming with electrical excitations. I have been inclined to look rather at circuits specifically designed for the express job of producing effects like pain, or High C or blue-yellow —circuits of the kind that one finds above a high transection of the spinal cord but not below, circuits with something that may well be present in the tiny pinhead dimensions of the midbrain of the color-perceiving goldfish but lacking in the massive spinal-cord tissue of the ox, circuits that are profoundly affected by certain lesions of the midbrain and thalamus but little altered by complete absence of the entire human cerebellum. Were it actually to come to laying our

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money on the line, I should probably bet, first choice, on still larger cerebral configurations, configurations that include the combined effect of both (a) the specialized circuit systems such as the foregoing plus (b) a background of cerebral activity of the alert, waking type. Take away either the specific circuit, or the background, or the orderly activity from either one, and the conscious effect is gone.

In this day of information explosion, these matters are not so much of the "ivory tower" as they used to be: To the engineer who comes around from Industrial Associates with dollars and cents in his eye and company competition in his heart the possibility is of more than theoretical interest that conscious awareness may be something that is not necessarily tied to living hardware, that it could prove to be an emergent, over-all circuit property that might, in theory, be borrowed and, given sufficient acreage, perhaps copied some day in order to incorporate pain and pleasure, sensations and percepts, into the rapidly evolving circuitry of computer intellect. When the aim is to build into your circuit systems some kind of negative and positive reinforcement, then pain and pleasure are about the best kind. And eager young theoreticians from the NASA committee or from radio astronomy already want a more educated guess about the possibility of encountering on other globes other minds with perhaps totally different dimensions of conscious awareness, and if not, why not? Then there are more imminent, practical matters such as the need, in view of certain other explosions we face, to be able to pinpoint the first appearance of consciousness in embryonic development and chart its subsequent growth and maturation.

Unless you are among those who still believe that value judgments lie outside the realm of science, you may probably agree that a few reliable answers in these general areas and their implications could shake considerably the going value systems of our whole culture.

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We shift now to certain lesser and subsidiary problems, but problems more approachable in research. Unlike the situation 25 years ago, most of us today are quite ready to talk about the evolution and inheritance not only of brain morphology but also of brain function, including general behavior and specific behavior traits. Earlier renunciation of the whole instinct concept in the animal kingdom generally stemmed in large part from our inability to imagine any growth mechanisms sufficiently precise and elaborate even to begin the fabrication of the complex nerve networks of behavior. This outlook was supported in the analytic studies of nerve growth all through the 1920's and 1930's which indicated that nerve fibers grow and connect in a random, diffuse, and non-selective manner governed almost entirely by indifferent, mechanical factors.

Today the situation is entirely changed. The supposed limitations in the machinery of nerve growth are largely removed in the new insight that we have obtained in recent years into the way in which the complicated nerve-fiber circuits of the brain grow, assemble, and organize themselves in a most detailed fashion through the use of intricate chemical codes under genetic control (Sperry, 1950a, 1950b, 1951, 1958, 1961, 1962, 1963). The new outlook holds that the cells of the brain are labeled early in development with individual identification tags, chemical in nature, whereby the billions of brain cells can thereafter be recognized and distinguished, one from another. These chemical differentials are extended into the fibers of the maturing brain cells as these begin to grow outward, in some cases over rather long distances, to lay down the complicated central communication lines. It appears from our latest evidence that the growing fibers select and follow specific prescribed pathways, all well marked by chemical guideposts that direct the fiber tips to their proper connection sites. After reaching their correct synaptic zones, the fibers then

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link up selectively among the local population with only those neurons to which they find themselves specifically attracted and constitutionally matched by inherent chemical affinities.

The current scheme now gives us a general working picture of how it is possible, in principle at least, for behavioral nerve nets of the most complex and precise sorts to be built into the brain in advance without benefit of experience. Being under genetic control, these growth mechanisms are of course inheritable and subject to evolutionary development. The same is true of the differential endogenous physiological properties of the individual cell units in these networks which, along with the morphological interconnections, are of critical importance in the shaping of behavior patterns. We have at present only the general outlines and general principles of the developmental picture; much of the detail has yet to be worked out. Also, the underlying chemistry of the demonstrated selectivity in nerve growth, as well as the molecular basis of the morphogenetic gradients involved, and of all the rest of the chemical "I. D. Card" concept remains a wide-open field that so far has been virtually untouched.

In connection with this emphasis on the "inherited" in brain organization, one may well question the extent to which the observed inbuilt order in the anatomical structure necessarily conditions functional performance and behavior. Some years ago, when we subscribed to the doctrine of an almost omnipotent adaptation capacity in the central nervous system and to functional equipotentiality of cortical areas and to the functional interchangeability among nerve connections in general (Sperry, 1958), Karl Lashley surmised that if it were feasible, a surgical rotation through 180 degrees of the cortical brain center for vision would probably not much disturb visual perception. Rotation of the brain center was not feasible, but it was possible to

rotate the eyes surgically through 180 degrees in a number of the lower vertebrates and also to invert the eyeball, by transplantation from one to the other orbit, on the up-down or on the front-back axis and also to cross-connect the right and left eyes to the wrong side of the brain (Sperry, 1950a). All these and different combinations thereof were found to produce very profound disturbances of visual perception that were correlated directly in each case with the geometry of the sensory disarrangement. The animals, after recovery from the surgery, responded thereafter as if everything were to them upside down and backward, or reversed from left to right, and so on. Contrary to earlier suppositions regarding the dynamics of perception and cortical organization, it appeared that visual perception was very closely tied indeed to the underlying inherited structure of the neural machinery.

We inferred further from nerve-lesion experiments (Sperry, 1950b) on the illusory spinning effects produced by these visual inversions that the inbuilt machinery of perception must include also certain additional central mechanisms by which an animal is able to distinguish those sensory changes produced by its own movement from those originating outside. The perceptual constancy of an environment in which an animal is moving, for example, or of an environment that it is exploring by eye, head, or hand movements, would seem to require that, for every movement made, the brain must fire "corollary discharges" into the perceptual centers involved. These anticipate the displacement effect and act as a kind of correction or stabilizing factor. These centrally launched discharges must be differentially gauged for the direction, speed, and distance of each move. Along with the dynamic schema for body position which the brain must carry at all times, these postulated discharges conditioning perceptual expectancy at every move would appear to be a very important feature of the

unknown brain code for perception. The consistent appearance of the spontaneous optokinetic reaction of inverted vision in fishes, salamanders, and toads would indicate that the underlying mechanism is basic and must have evolved very early.

Since the representation of movement at higher cortical levels generally seems to be more in terms of the perceptual expectancy of the end effect of the movement than in terms of the actual motor patterns required to mediate the movement, the postulated "corollary discharges" of perceptual constancy may not involve so much of an additional load, in terms of data processing, as might at first appear.

We are ready now for that old question: How much of brain organization and behavior should we blame or credit to inheritance and how much to learning and experience? As far as we can see now, it seems fair to say that all that central nervous organization that is illustrated and described in the voluminous textbooks, treatises, and professional journals of neuro-anatomy, that is, all the species-constant patterning of brain structure, the micro-architecture as well as the gross morphology that has so far been demonstrated anatomically, seems to be attributable to inheritance. Another way of saying the same thing is that no one has yet succeeded in demonstrating anatomically a single fiber or fiber connection that could be said with assurance to have been implanted by learning. In this same connection, it is entirely conceivable (though not particularly indicated) that the remodeling effects left in the brain by learning and experience do not involve the addition or subtraction of any actual fibers or fiber connections but involve only physiological, perhaps membrane, changes that effect conductance or resistance to impulse transmission, or both, all within the existing ontogenetically determined networks.

The foregoing picture leaves plenty of room for learning and for the combined effects of learning plus maturation

during that prolonged period in human childhood when these two factors overlap. Nevertheless the present picture represents a very considerable shift of opinion over the past two decades in the direction of inheritance.

Some of you may find certain aspects here a bit difficult to reconcile with other inferences drawn in recent years from a series of sensory deprivation studies on mammals in which cats, monkeys, chimpanzees, and other animals have been raised in the dark or with translucent eye caps or in harnesses or holders of various sorts and in which, as a result of the various kinds of deprivation of experience in their early development the animals came to show subsequent deficits, moderate to severe, in their perceptual or motor capacities. The tendency to interpret these findings, along with those from human cataract cases, as evidence of the importance of early learning and experience in shaping the integrative organization of the brain we have long felt to have been overdone (Sperry, 1950a, 1962). In nearly all cases the findings could be equally well explained on the assumption that the effect of function is simply to maintain, or to prevent the loss of, neural organization already taken care of by growth. What the results have come to show in many of these studies is that certain of the newly formed neuronal elements, if abnormally deprived of adequate stimulation, undergo an atrophy of disuse. In much the same way cells of the skeletal muscles differentiate in development to the point at which they are contractile and ready to function, but then they too atrophy and degenerate if not activated. This basic developmental "use-dependent" property in maturing neurons, or even some evolutionary derivative of it, applied farther centrally beyond the sensory paths amid more diffuse growth pressures, especially among cortical association units, could, however, have true patterning effects and become a definitely positive factor in learning and imprinting.

We have been approaching very closely here the general problem of memory. Among brain functions, memory certainly rates as one of the prime "problems outstanding." Whatever the nature of the neural mechanism underlying memory, it seems to have appeared quite early in evolution. (Some writers say that even flatworms have memory!) We are frequently impressed in our own work with learning and memory in cats, and even in fishes, with the fact that their simple memories, once implanted, seem to be strong and lasting. With respect to memory, then, what separates the men from the animals is very likely not so much the nature of the neural trace mechanism as the volume and the kind of information handled. The problems that relate to the translation and coding of mental experience, first into the dynamics of the brain process, and then into the static, frozen, permanent trace or engram system, pose the more formidable aspects of the memory problem.

Fundamental to these memory questions, as also to the problems of perception, volition, learning, motivation, and most of the higher activities of the nervous system, is that big central unknown that most of us working on the higher properties of the brain keep tangling with and coming back to. You may find it referred to variously as: the "brain code," or the "cerebral correlates of mental experience," or the "unknown dynamics of cerebral organization," or the "intermediary language of the cerebral hemispheres," or, in some contexts, just the "black box." Thus far we lack even a reasonable hypothesis regarding the key variables in the brain events that correlate with even the simplest of mental activities, such as the elementary sensations or the simple volitional twitch of one's little finger.

In our own efforts to help to chip away at this central problem of the language of the hemispheres, we have been trying for some 10 years first to divide the problem in half by splitting the brain down the middle before we start to study

it. (Many times we wonder if the end effect of this split brain approach is not so much to halve our problems as it is to double them.) At any rate, the brain-bisection studies leave us with a strong suspicion that evolution may have saddled us all with a great deal of unnecessary duplication, both in structure and in the function of the higher brain centers.

Space in the intracranial regions is tight, and one wonders if this premium item could not have been utilized for better things than the kind of right-left duplication that now prevails. Evolution, of course, has made notable errors in the past, and one suspects that in the elaboration of the higher brain centers evolutionary progress is more encumbered than aided by the bilateralized scheme which, of course, is very deeply entrenched in the mechanisms of development and also in the basic wiring plan of the lower nerve centers.

Do we really need two brain centers, for example, to tell us that our blood sugar is down or our blood pressure is up, or that we are too hot or too cold, and so on? Is it necessary to have a right and also a left brain center to let us know that we are sleepy or angry, sad or exuberant, or that what we smell is Arpege or what we taste is salty or that what we hear is voices, and so on and on and on? Surely most of us could manage to get along very well with only one cerebral anxiety mechanism, preferably in the minor hemisphere.

Emotion, personality, intellect, and language, among other brain business, would seem by nature to be quite manageable through a single unified set of brain controls. Indeed, the early loss of one entire hemisphere in the cat, monkey, and even in man causes amazingly little deficit in the higher cerebral activities in general.

With the existing cerebral system, most memories as well have to be laid down twice—one engram for the left

hemisphere and another engram copy for the right hemisphere. The amount of information stored in memory in a mammalian brain is a remarkable thing in itself; to have to double it all for the second hemisphere would seem in many ways a bit wasteful. It is doubtful that all this redundancy has had any direct survival value (unless evolution could have foreseen that neurologists would be opening and closing the cranium to produce brain lesions under careful aseptic conditions that permit survival).

In the human brain, of course, we begin to see definite evidence of a belated tendency in evolution to try to circumvent some of the duplication difficulties. A de-duplication trend is seen particularly in the lateralization of speech and writing within the single dominant hemisphere in the majority of persons. Speech, incidentally, is another essentially symmetrical activity for which a double right and left control is quite unnecessary, even at the lower levels of the motor hierarchy. When the brain does try in some individuals to set up two central administrations for speech, one in each hemisphere, the result tends to make for trouble, like stammering and a variety of other language difficulties.

The fact that the corpus callosum interconnecting the two cerebral hemispheres is so very large and the functional damage produced by its surgical section is so very minor in most ordinary activities seems to be explainable in part by the fact that the great cerebral commissure is a system for cross communication between two entities that to a large extent are each completely equipped and functionally self-sufficient. The corpus callosum appears late in evolution, being essentially a mammalian structure, and its development is closely correlated with the evolutionary elaboration of the neocortex of the mammalian cerebral hemispheres.

Accordingly it is not surprising that it is in the human

brain, and particularly in connection with speech, that the functional effects produced by surgical disconnection of the two cerebral hemispheres become most conspicuous. During the past two years we have had an opportunity to test and to study two patients, formerly unmanageable epileptics, who have had their right and left hemispheres disconnected by complete section of the corpus callosum, plus the anterior commissure, plus the hippocampal commissure, plus the massa intermedia, in what is perhaps the most radical surgical approach to epilepsy thus far undertaken. The surgery was done by Drs. Philip J. Vogel and Joseph E. Bogen (see Bogen and Vogel, 1962) of Los Angeles.[1]

It seemed a reasonable hope, in advance, that such surgery might help to restrict the seizures to one hemisphere and hence to one side of the body, and possibly to the distal portions of arm and leg, since voluntary control of both sides of the head, neck, and trunk tends to be represented in both hemispheres. In our colony of split-brain monkeys that have had similar surgery, we not uncommonly see epileptic-like seizures, especially during the early weeks after brain operations, and these seizures show a definite tendency to center in the distal extremities of the arm and leg and to be restricted to one side. It also seemed reasonable that this surgery might help the patients to retain consciousness in one hemisphere during an attack, if not throughout, at least during the early stages, and thereby give them a chance to do things that might help to break

or control the seizures, or at a minimum to allow time in which to undertake protective measures before the second side became involved. It was further hoped that such surgery might reduce the severity of the attacks by the elimination of a very powerful avenue for the right-left mutual reinforcement of the seizures during the generalized phase, especially during *status epilepticus,* which was of major concern in both the cases cited above.

Judged from earlier reports of the cutting of the corpus callosum and from the behavior of dozens of monkeys that we have observed in the laboratory with exactly the same surgery (Sperry, 1961, 1964), it seemed unlikely that this kind of surgery would produce any severe handicap, or surely none so bad as certain other forms of psychosurgery that have been used on a much more extensive scale. That the surgery might decrease the incidence of the seizures to the point of virtually eliminating them (as it seems to have done so far in both cases) was unexpected; our fingers remain very much crossed on this latter point.

Everything that we have seen so far indicates that the surgery has left each of these people with two separate minds, i.e., with two separate spheres of consciousness (Gazzaniga, Bogen, and Sperry, 1962, 1963). What is experienced in the right hemisphere seems to be entirely outside the realm of awareness of the left hemisphere. This mental duplicity has been demonstrated in regard to perception, cognition, learning, and memory. One of the hemispheres, the left, dominant, or major hemisphere, has speech and is normally talkative and conversant. The other mind of the minor hemisphere, however, is mute or dumb, being able to express itself only through non-verbal reactions; hence mental duplicity in these people following the surgery, but no double talk.

Fortunately, from the patients' standpoint, the functional separation of the two hemispheres is counteracted by a large

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number of unifying factors that tend to keep the disconnected hemispheres doing very much the same thing from one part of the day to the next. Ordinarily, a large common denominator of similar activity is going in each. When we deliberately induce different activities in right and left hemispheres in our testing procedures, however, it then appears that each hemisphere is quite oblivious to the experiences of the other, regardless of whether the going activities match or not.

This is illustrated in many ways: For example, the subject may be blindfolded, and a familiar object such as a pencil, a cigaret, a comb, or a coin is placed in the left hand. Under these conditions, the mute hemisphere connected to the left hand, feeling the object, perceives and appears to know quite well what the object is. It can manipulate it correctly; it can demonstrate how the object is supposed to be used; and it can remember the object and go out and retrieve it with the same hand from among an array of other objects. While all this is going on, the other hemisphere has no conception of what the object is and says so. If pressed for an answer, the speech hemisphere can only resort to the wildest of guesses. So the situation remains just so long as the blindfold is kept in place and other avenues of sensory input from the object to the talking hemisphere are blocked. But let the right hand cross over and touch the test object in the left hand; or let the object itself touch the face or head as in the use of a comb, a cigaret, or glasses; or let the object make some give-away sound, such as the jingle of a key case, then immediately the speech hemisphere produces the correct answer.

The same kind of right-left mental separation is seen in tests involving vision. Recall that the right half of the visual field and the right hand are represented together in the left hemisphere and vice versa. Visual stimuli such as pictures, words, numbers, and geometric forms flashed on a

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screen directly in front of the subject and to the right side of a central fixation point are all described and reported correctly with no special difficulty. On the other hand similar material flashed to the left half of the visual field is completely lost to the talking hemisphere. Stimuli flashed to one half field seem to have no influence whatever, in tests to date, on the perception and interpretation of stimuli presented to the other half field.

Note in passing that these disconnection effects do not show up readily in ordinary behavior. They must be demonstrated by the flashing of the visual material fast enough so that eye movements cannot be used to sneak the answers into the wrong hemisphere, or in the testing of right and left hands vision must be excluded with a blindfold, auditory cues eliminated, and the hands kept from crossing, and so on. One of the patients, a 30-year old housewife with two children, goes to market, runs the house, cooks the meals, watches television, and goes out to complete, three-hour shows at the drive-in theater, all without complaining of any particular splitting or doubling in her perceptual experience. Her family believes that she still does not have so much initiative as formerly in her housecleaning, in which she was meticulous, and that her orientation is not so good, for example, she does not find her way back to the car at the drive-in theater as readily as she formerly could. In the early months after surgery there appeared to be definite difficulty with memory. By now, some eight months later, there seems to be much improvement in this regard, though not complete recovery. Involvement of the fornix would have to be ruled out before effects like the latter can be ascribed to the commissurotomy.

In the visual tests again, one finds plenty of evidence that the minor, dumb, or mute hemisphere really does perceive and comprehend, even though it cannot express verbally what it sees and thinks. It can point out with the left hand

a matching picture from among many others that have been flashed to the left field, or it can point to a corresponding object that was pictured in the left-field screen. It can also pick out the correct written name of an object that it has seen flashed on the screen, or vice versa. In other words, Gazzaniga's more recent results show that the dumb left hemisphere in the second patient is not exactly stupid or illiterate; it reads a word such as "cup," "fork," or "apple" flashed to the left field and then picks out the corresponding object with the left hand. While the left hand and its hemisphere are thus performing correctly, however, the other hemisphere, again, has no idea at all which object or which picture or which name is the correct one and makes this clear through its verbal as well as other responses. You regularly have to convince the talking hemisphere to keep quiet and to let the left hand go ahead on its own, in which case it will usually pick out the correct answer.

These minor differences of opinion between the right and left hemispheres are seen rather commonly in testing situations. For example, the left hand is allowed to feel and to manipulate, say, a toothbrush under the table or out of sight behind a screen. Then a series of five to 10 cards are laid out with names on them such as "ring," "key," "fork." When asked, the subject may tell you that what she felt in the left hand was a "ring." However, when instructed to point with the left hand, the speechless hemisphere deliberately ignores the erroneous opinions of its better half and goes ahead independently to point out the correct answer, in this case the card with the word "toothbrush."

As far as we can see, about the only avenue remaining for direct communication between mind-right and mind-left is that of extrasensory perception. If any two minds should be able to tune in on each other, one might expect these two to be able to do so, but thus far no evidence of such effects is apparent in the test performances.

The conscious awareness of the minor hemisphere produced by this vertical splitting of the brain often seems so remote to the conversant hemisphere as to be comparable perhaps to that produced by a spinal transection. To go back here to some of the issues on which we started, one wonders if we can really rule out, as I implied above, the alternative contention of those who maintain that spinal cords, loaves of bread, and even single molecules have a kind of consciousness. Either way, the inferences to be drawn regarding the evolution and elaboration of consciousness for most practical purposes remain much the same.

We are often asked if each of the disconnected hemispheres must not also have a will of its own and if the two do not then get into conflict with each other. In the first half year after surgery, particularly with the first patient, we got reports suggesting something of the kind. For example, while the patient was dressing and trying to pull on his trousers, the left hand started to work against the right, pulling them off again. Or, the left hand, after just helping to tie the belt of his robe, went ahead on its own to untie the completed knot, whereupon the right hand would have to supervene again to get it retied. The patient and his wife used to refer to the "sinister left hand" which sometimes tried to push the wife away aggressively at the same time that the hemisphere of the right hand was trying to get her to come and help him with something. These antagonistic movements of right and left hands are fairly well restricted to situations in which the reactions of left and right hand are easily made from the same common supporting posture of body and shoulders. Generally speaking, there are so many unifying factors in the situation and functional harmony is so strongly built into the undivided brain stem and spinal networks, by express design, that one sees little overt expression or overflow into action, at least, of conflicting will power.

This matter of having two free wills packed together inside the same cranial vault reminds us that, after consciousness, free will is probably the next most treasured property of the human brain. Questions and information relating to the evolution of free will have practical impact rating right at the top, along with those of consciousness. As such it probably deserves at least a closing comment. Some maintain that free will is an evolved, emergent property of the brain that appeared between man and the higher apes, or, depending on whom you read, maybe somewhere after bacteria perhaps, but before houseflies.

Unlike "mind," "consciousness," and "instinct," "free will" has made no comeback in behavioral science in recent years. Most behavioral scientists would refuse to list free will among our problems outstanding, or at least as an unanswered problem. (To agree that behavior is unlawful in this respect might put them out of work as scientists, you see, and oblige them perhaps to sign up with the astrologers' union.) Every advance in the science of behavior, whether it has come from the psychiatrist's couch, from microelectrode recording, from brain-splitting, or from the running of cannibalistic flatworms, seems only to reinforce that old suspicion that free will is just an illusion. The more we learn about the brain and behavior, the more deterministic, lawful, and causal it appears.

In other words, behavioral science tells us that there is no reason to think that any of us here tonight had any real choice to be anywhere else, or even to believe in principle that our presence here was not already "in the cards," so to speak, five, 10, or 15 years ago. I do not feel comfortable with this kind of thinking any more than you do, but so far I have not found any satisfactory way around it. Alternatives to the rule of causal determinism in behavior proposed so far, like the inferred unlawfulness in the dance of subatomic particles, seem decidedly more to be deplored as a solution

than desired.

The above statements are not to say that, in the practice of behavioral sciences, we must regard the brain as just a pawn of the physical and chemical forces that play in and around it. Far from it. To go back to the beginning of the present lecture, recall that a molecule in many respects is the master of its inner atoms and electrons. The latter are hauled and forced about in chemical interactions by the over-all configurational properties of the whole molecule. At the same time, if our given molecule is itself part of a single-celled organism such as paramecium, it in turn is obliged, with all its parts and its partners, to follow along a trail of events in time and space determined largely by the extrinsic over-all dynamics of *Paramecium caudatum*. When it comes to brains, remember that the simpler electric, atomic, molecular, and cellular forces and laws, though still present and operating, have been superseded by the configurational forces of higher-level mechanisms. At the top, in the human brain, these include the powers of perception, cognition, reason, judgment, and the like, the operational, causal effects and forces of which are equally or more potent in brain dynamics than are the outclassed inner chemical forces.

You sense the underlying policy here: "If you can't lick 'em, join 'em," or, as Confucius might say, "If fate inevitable, relax and enjoy," or, "There may be worse fates than causal determinism." Maybe, after all, it is better to be embedded firmly in the causal flow of cosmic forces, as an integral part thereof, than to be on the loose and out of contact with these forces, "free floating" as it were and with behavioral possibilities that have no antecedent cause and hence no reason, nor any reliability when it comes to future plans, predictions, or promises.

And on this same theme, just one final point: If you were assigned the task of trying to design and build the perfect

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free-will model (let us say the perfect, all-wise, decision-making machine to top all competitors' decision-making machines), consider the possibility that your aim might not be so much to free the machinery from causal contact, as the opposite, that is, to try to incorporate into your model the potential value of universal causal contact; in other words, contact with all related information in proper proportion—past, present, and future.

It is clear that the human brain has come a long way in evolution in exactly this direction when you consider the amount and the kind of causal factors that this multidimensional intracranial vortex draws into itself, scans, and brings to bear on the process of turning out one of its "preordained decisions." Potentially included, thanks to memory, are the events and collected wisdom of most of a human lifetime. We can also include, given a trip to the library, the accumulated knowledge of all recorded history. And we must add to all the foregoing, thanks to reason and logic, much of the future forecast and predictive value extractable from all these data. Maybe the total falls a bit short of universal causal contact; maybe it is not even quite up to the kind of thing that evolution has going for itself over on Galaxy Nine; and maybe, in spite of all, any decision that comes out is still predetermined. Nevertheless it still represents a very long jump in the direction of freedom from the primeval slime mold, the Jurassic sand dollar, or even the latest 1964-model orangutan.

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JAMES ARTHUR LECTURE ON
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EVOLUTION OF PHYSICAL
CONTROL OF THE BRAIN

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Harry Grundfest, *Specialization and Evolution of Bioelectric Activity;* May 28, 1963

Roger W. Sperry, *Problems Outstanding in the Evolution of Brain Function;* June 3, 1964

José M. R. Delgado, *Evolution of Physical Control of the Brain;* May 6, 1965

EVOLUTION OF PHYSICAL
CONTROL OF THE BRAIN

INTRODUCTION

I would like to express my gratitude for the privilege of addressing this distinguished audience, and also my feeling of responsibility in following so many illustrious predecessors and in honoring the founder of the James Arthur Lectures on the Evolution of the Human Brain. The topics covered by earlier speakers in this series have included behavioral implications derived from cerebral anatomy and physiology, neurophysiological problems, comparative anatomy, embryology, and fossil skulls. In this year's lecture, I would like to project cerebral evolution toward the future without losing touch with the solid ground of experimentation.

The human brain has evolved with a functional asymmetry which may be responsible for some of the conflicts of our present age. Apparently it has been easier for man to direct his attention outward to the environment than inward to deal with the complexity of his own mental structure, and easier to understand and manipulate Nature than to control his own behavior. In prehistoric times, and even today in primitive societies, man was and is at the mercy of the elements. When disaster struck, and floods, pestilence, or hunger desolated the land, the only possible reactions were fatalistic resignation, appeal to supernatural powers, or despair. Modern civilization has progressed so much in the understanding and domination of the physical world, that relations between man and Nature have been completely transformed. Technology is reshaping the face of the earth,

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but the greatest change has taken place in the human brain which is now filled with new formulas, theories, and knowledge, and empowered with a new attitude of confidence toward natural forces which are no longer the masters but are becoming the servants of man. The expanding sciences have directed most of our present intellectual and economic power toward industry, biology, electronics, atomic energy, outer space, and similar fields of endeavor, while only a minor fraction is devoted to inquiry into the roots of mental faculties. This unbalanced interest has an explanation. When observation and reason were the main tools for the acquisition of knowledge, philosophical speculation flourished. When the discovery of new methods permitted the scientific exploration of Nature, the study of subjects beyond experimental reach was neglected. Certainly, the disciplines of psychology and psychiatry have greatly expanded in our century, but a perusal of the literature shows that until one or two decades ago, the brain was treated as a "black box" which could be reached only through the senses. Psychological investigations analyzed correlations between sensory input and behavioral output, but it was not possible to explore the processes lying in between which were hidden in the mystery of brain physiology.

During the last decade we have reached an historical turning point because of the development of methods which permit the coordination and synthesis of physical, physiological, pharmacological, and psychological research. As will be explained in the following pages, science has developed a new electrical methodology for the study and control of cerebral functions in animals and humans. Learning, emotions, drives, memory, consciousness, and other phenomena which in the past belonged only in the realm of philosophy are now the subjects of neurophysiological experimentation. In the last few years, the scalpel of the brain

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surgeon has modified psychological reactions and a wealth of wonder drugs has liberated many patients from mental institutions.

I am not so naive as to think that cerebral research holds all the answers to mankind's present problems, but I do believe that an understanding of the biological bases of social and antisocial behavior and of mental activities, which for the first time in history can now be explored in the conscious brain, may be of decisive importance in the search for intelligent solutions to some of our present anxieties, frustrations, and conflicts. Also, it is essential to introduce a balance into the future development of the human mind, and I think that we now have the means to investigate and to influence our own intellect.

In support of these ideas, I shall present a brief outline of the evolution of the physical control of cerebral processes, followed by several examples of our incipient control of behavioral mechanisms, and I will end with a discussion of the principles and implications involved.

HISTORICAL OUTLINE: THEORETICAL AND METHODOLOGICAL EVOLUTION

ANIMAL EXPERIMENTATION

For many centuries it was accepted that fluids or "animal spirits" were the cause of muscle contraction (Galen, 130 to *ca.* 200 A.D.), until the famous controversy between the schools of Luigi Galvani (1737–1789) and Alessandro Volta (1745–1827) focused the attention of nineteenth-century scientists and philosophers on the possible physical control of some manifestations of life. Contractions produced in a frog nerve-muscle preparation by touching it with a bimetallic arc were interpreted by Galvani as proof of the existence of animal electricity, while Volta believed that the electrical source was in the contact of two dissimilar

metals. This controversy was resolved when Alexander von Humboldt (1769–1859) demonstrated that animal electricity and bimetallic electricity were co-existing phenomena. Leg movements evoked in frogs by the inanimate force of electricity proved that muscle contraction could be induced independently of the "principle of life" which had been considered the essential mover of all biological activities. The discovery that living organs could be influenced by instrumental manipulations directed by the will of a human being brought about a revision of the traditional concepts of vitalism which were challenged at that time by Emil DuBois-Reymond (1818–1896) and other scientists. The romantic mystery of the soul's "animal spirits" which had dominated biology for almost 2000 years now gave place to more prosaic chemical and physical laws, and even nervous activity could be investigated experimentally. DuBois-Reymond not only discovered many basic neurophysiological principles, including action current, polarization, electrogenesis, and propagation of the nerve impulse; he also provided the technical means for study of the two most fundamental processes of neural activity by inventing the galvanometer for the detection of electrical currents and the induction coil for faradic excitation of nervous tissue. At that time, the possibility of exciting the spinal cord and brain stem by other than physiological stimuli was violently debated, and the excitability of the brain was completely denied. Then Fritsch and Hitzig (1870) performed a beautiful series of experiments, applying galvanic stimulations to the exposed cerebral cortex of anesthetized dogs. Excitations of the posterior part of the brain failed to evoke motor effects, but in the anterior region contralateral body and limb movements were elicited. Weak currents induced discrete contractions localized to specified muscle groups, while stronger currents increased the strength and spread

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of the evoked responses; if the intensity was further augmented, generalized convulsions appeared.

The scientific impact of these studies, and also the successful clinical localization of speech functions by Broca (1824–1880), promoted great interest in cerebral mapping, based on regional ablation and electrical stimulation studies attempting to pin precise functional labels to specific anatomical structures. Fortunately, there was much less speculation and much more experimentation in these studies than in the discredited phrenology, and, in spite of controversial issues, many of the facts discovered in the last century have remained important scientific contributions.

One of the main handicaps in these investigations was the need for opening the skull and exposing the brain. Operations were usually performed under general anesthesia which blocked pain perception but also blocked some of the most important functions of the nervous system. Emotions, consciousness, and intelligence were certainly absent in heavily sedated animals or in the isolated nerves of the squid, and for many years scientists directed their attention to sleeping brains and overlooked the complexity of awake minds. Textbooks of cerebral physiology were concerned with synapses, pathways, reflexes, posture, and movement, while mental functions and behavior were considered to belong to a different discipline.

Some pioneer efforts, however, were directed toward exploration of the waking brain, and techniques were devised for the introduction of wires through the skull in order to apply electrical currents to the brains of conscious animals. In 1898, Ewald had the idea of screwing an ivory cone into the skull of an anesthetized dog, and the following day, when operative anesthesia had worn off, electrodes were inserted into the brain through the ivory piece. A leash around the animal's neck contained stimulating wires, and

a small dry-cell battery carried by the observer served as the electrical source. Although the technique and results were primitive, a way had been found to investigate the brain in awake animals. The technique of intracerebral electrodes was dormant for many years until Hess (1932) developed his own method to explore the hypothalamus and other cerebral areas in unanesthetized cats. In a series of brilliant experiments, Hess demonstrated that autonomic functions, posture, equilibrium, movement, sleep, and even fear and aggressiveness may be influenced by electrical stimulation of specific cerebral structures. For the first time, it was revealed that psychological manifestations like rage do not depend exclusively on sensory inputs and physiological stimuli, but can be induced by electrical currents applied directly to the brain. Although these findings did not produce a significant impact on philosophical thinking, in retrospect they may be considered as important as the nineteenth-century demonstration that the contraction of a frog muscle did not depend on circulating spirits and could be controlled by physical instrumentation.

For two decades, the methods of Hess attracted only limited interest among biologists, but in the 1950's, there was a sudden expansion of the new disciplines of psychosurgery, psychosomatic medicine, psychopharmacology, and physiological psychology, and many investigators realized the great research potential of intracerebral methods for the study of behavioral-cerebral correlations in awake animals. With this increased interest, a variety of technical improvements appeared. Electrodes were no longer introduced free-hand into the brain, but were inserted with geometric precision with the aid of micromanipulators and stereotaxic coordinates. Anatomical maps of the depths of the brain were compiled for rats, cats, dogs, and monkeys. Aseptic precautions and instrumental refinements permitted

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long-term implantation of electrodes, which in some cases lasted for several years. The sight of experimental animals with sockets on top of their heads was exceptional in 1950 but had spread to hundreds of laboratories around the world by 1960. Electrodes were implanted not only in the usual laboratory animals, but also in other species, including crickets, roosters, chimpanzees, dolphins, and brave bulls.

Experiments were generally performed under some restraint. Rats were convenient subjects because of their behavioral simplicity, and they were not disturbed by a light coil of wires connecting their terminal head sockets with the stimulators. In this way, the brain was stimulated in fully conscious rats while they pressed levers, ran mazes, and maneuvered with considerable freedom, being limited only by the length of the leads and the size of the cage. A similar set-up was also used successfully with cats, providing they were peaceful and tame. These studies were often extended for months and were very appropriate for the investigation of autonomic, somatic, and behavioral effects evoked by electrical stimulation of the brain, and also for the analysis of electrical recordings taken during spontaneous or induced activities. The combination of intracerebral electrodes with other physiological and psychological techniques was very fruitful and showed that animals can learn to perform instrumental responses to seek or avoid stimulation of determined cerebral structures. Scientific exploitation of these techniques continues today with universal acceptance, as shown by current scientific literature.

The use of electrodes in monkeys presented a greater challenge because of their destructive skills and restless curiosity. A heavy protection of the connecting leads was necessary when the animal was observed on a testing table. In other cases, the monkey was placed in a special restrain-

ing chair where it could manipulate levers and feed itself without being able to reach the terminal sockets on its head. In these situations, conditioning and psychological testing were successfully performed, but spontaneous behavior was naturally curtailed.

The connecting leads trailing behind each animal were a serious handicap for behavioral studies and were unsuitable for use in chronic stimulations or investigations of group activities. The obvious solution was to use remote-controlled instrumentation, with a receiver carried by the animal and activated by induction or by radio. Several stimulators of this type have been proposed in the last 30 years (see bibliography in Delgado, 1963b), but solutions to many of the technical problems involved were not found until recently, when the development of transistors and electronic miniaturization permitted the construction of small, practical, and reliable cerebral radio stimulators (Delgado, 1963b). After a considerable amount of trial and error, and in spite of the primates' genius for destroying any equipment within reach, monkey-proofing of instruments was achieved (figs. 3, 4, 5). The use of radio stimulators allowed the excitation of cerebral structures in completely free animals engaged in normal activities within an established colony and unaware of the scientist's manipulations. In this way, the role of specific areas of the brain in social relations was investigated. At the same time, blood pressure, body temperature, electrical activity of the heart and brain, and other physiological variables could be recorded by radio telemetry. In addition, individual and social behavior have been continuously recorded, day and night, by time-lapse photography. Radio techniques represented an important step toward physical control of the brain, providing an essential tool for behavioral studies, and it may safely be predicted that within a few years telestimulation will spread

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to most brain research institutes. We can also expect that new developments in micro-electronics, including integrated circuits and thin film techniques, will facilitate the construction of multi-channel radio-activated stimulators reduced in size to a few millimeters. The limits of brain control do not seem to depend on electronic technology but on the biological properties of living neurons.

Among possible physiological handicaps, the presence of electrodes and repeated applications of electricity could be disrupting factors for the normality of the nerve cells. Insertion of electrodes into the brain substance is certainly a traumatic procedure which destroys neural tissue and produces local hemorrhage, followed by inflammation, foreign body reaction, and the formation of a glial capsule 0.1– 0.2 mm. thick around the inserted wires. All of this reactive process is limited to a very small area measured in tenths of millimeters, and there is no evidence of functional disturbance in the neighboring neurons. Beyond the electrode tract, the brain appears histologically normal and electrodes seem to be well tolerated, as judged by the absence of abnormal electrical activity, by the reliability of effects evoked by electrical stimulation, and by the consistency of thresholds through months of experimentation (Delgado, 1955b). The longest reported implantation time of electrodes in the brain has been over four years, in a rhesus monkey.

From the functional point of view, two aspects should be considered in implantation experiments. The first is related to fatigability and the second to lasting functional changes. Physiological textbooks state that motor effects produced by electrical stimulation of the cerebral cortex fade away in a few seconds, and that a rest period of about one minute is necessary before the cortex recovers its excitability. If this were true throughout the brain, electricity could not

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be effectively used for control of cerebral function. However, experimentation has shown that the fatigability of some areas is slow or negligible. In monkeys, the putamen has been stimulated for more than 30 minutes without diminution of the elicited postural changes, and the hypothalamus has been excited for days without fatigue of the evoked pupillary constriction. Red nucleus stimulation repeated every minute for 14 days has evoked reliable and consistent sequential responses. Thus, while a few areas of the brain show quick fatigability, it should be recognized that many others can be stimulated effectively for minutes or even days. The evoked effects generally have lasted only as long as the stimulation, but in some cases enduring after-effects have been obtained. In the cat, programmed intermittent stimulations of the amygdala for one hour daily evoked bursts of high-voltage fast activity and other signs of increased electrical activity, along with changes in spontaneous behavior which outlasted stimulation periods for many hours and occasionally for days. In other studies, excitation of the basolateral nucleus of the cat's amygdala for only 10 seconds inhibited food intake for minutes, and, in one case, the inhibitory effect persisted for three days (Fonberg and Delgado, 1961). These findings together with extensive experimentation by many authors have demonstrated that intracerebral electrodes are safe and can be tolerated for years, providing an effective tool for sending and recording electrical impulses to and from the brain of unanesthetized animals.

ELECTRODES IN THE HUMAN BRAIN

With the background of animal experimentation, it was natural that some investigators should contemplate the implantation of electrodes inside the human brain. Neurosurgeons had already proved that the central nervous sys-

tem is not so delicate as most people believe, and during therapeutic surgery parts of cerebral tissue had been cut, frozen, cauterized, or ablated with negligible adverse effects on the patient. Exploratory introduction of needles into the cerebral ventricles was a well-known and relatively safe clinical procedure, and, as electrodes are smaller in diameter than these needles, their introduction into the brain tissue should be even less traumatic. Implantation of electrodes inside the human brain offered the opportunity for prolonged electrical exploration which could be decisive for several diagnostic and therapeutic procedures. For example, when brain surgery and ablation are contemplated in patients suffering from epileptic attacks, it is essential to identify the focal areas of abnormal electrical activity. Electrodes may remain in place for days or weeks, during which spontaneous seizures can be recorded and detailed exploration repeated as many times as necessary. In other cases, intracerebral electrodes have been used to deliver intermittent stimulations for periods of days or even months (Feindel, 1961; Heath, 1954; King, 1961; Sem-Jacobsen et al., 1956; Walker and Marshall, 1961). Similar procedures have also been used in patients with intractable pain, anxiety neurosis, and involuntary movement. These therapeutic possibilities should be considered rather tentative, but accumulated experience has shown that electrodes are well tolerated by the human brain for periods of at least one year and a half, and that electrical stimulations may induce a variety of responses, including changes in mental functions, as will be explained later. The prospect of leaving wires inside the thinking brain could seem barbaric, uncomfortable, and dangerous, but actually the patients who have undergone this experience have had no ill effects, and they have not been concerned about the idea of being wired or by the existence of leads in their heads.

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In some cases, they enjoyed a normal life as out-patients, returning to the clinic for periodic stimulations. Some of the women proved the adaptability of the feminine spirit to all situations by designing pretty hats to conceal their electrical headgear.

The use of electrodes in the human brain is part of the present medical orientation toward activation of physiological mechanisms by electronic instrumentation, which already extends to several organs of the body. The clinical success of electrical driving of cardiac functions in man has been widely acclaimed. In spite of the delicacy and continuous mobility of the heart, stainless steel leads have been sutured to it, and in cases of block in the cardiac conduction system, artificial electronic pacemakers have been able to regulate heart rhythm, saving the lives of many patients. The bladder has been stimulated by implanted electrodes to induce urination in patients with permanent spinal block, and paralyzed limbs have been activated by programmed stimulators. A method has recently been described for placing leads in the auditory nerve to circumvent deafness caused by inner ear damage. Driving malfunctioning organs is simpler than attempting to direct the awake brain where millions of neurons are functioning and firing simultaneously for different purposes, but the expected results in this case are even more interesting. Exploring intracerebral physiology, we are reaching not only the soma but also for the psyche itself. Cerebral functions are usually classified in three groups: autonomic, somatic, and psychic, and in the following pages I shall discuss present experimental evidence for their electrical control.

TABLE OF HISTORICAL EVOLUTION
OF PHYSICAL CONTROL OF THE BRAIN

FINDINGS	IMPLICATIONS
Frog muscle contracted when stimulated by electricity. Volta, Galvani, DuBois-Reymond; 1780, 1800, 1848	"Vital spirits" are not essential for biological activities. Electrical stimuli under man's control can initiate and modify vital processes
Electrical stimulation of the brain in anesthetized dog evoked localized body and limb movements. Fritsch and Hitzig, 1870	The brain is excitable. Electrical stimuli of the cerebral cortex can produce movements
Stimulation of the diencephalon in unanesthetized cats evoked well-organized motor effects and emotional reactions. Hess, 1932	Motor and emotional manifestations may be evoked by electrical stimulation of the brain in awake animals
In single animals, learning, conditioning, instrumental responses, pain, and pleasure have been evoked or inhibited by electrical stimulation of the brain in rats, cats, and monkeys. See bibliography in Sheer, 1961	Psychological phenomena may be controlled by electrical stimulation of specific areas of the brain
In colonies of cats and monkeys, aggression, dominance, mounting, and other social interactions have been evoked, modified, or inhibited by radio stimulation of specific cerebral areas. Delgado, 1955a, 1964	Social behavior may be controlled by radio stimulation of specific areas of the brain
In patients, brain stimulations during surgical interventions or with electrodes implanted for days or months have blocked the thinking process, inhibited speech and movement, or in other cases have evoked pleasure, laughter, friendliness, verbal output, hostility, fear, hallucinations, and memories. See bibliography in Ramey and O'Doherty, 1960	Human mental functions may be influenced by electrical stimulation of specific areas of the brain

SUMMARY: Autonomic and somatic functions, individual and social behavior, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and in man, by electrical stimulation of specific cerebral structures. Physical control of many brain functions is a demonstrated fact, but the possibilities and limits of this control are still little known.

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Several areas of the brain play important roles in the regulation of visceral activity, and extensive studies have shown that electrical stimulation of the hypothalamus and other cerebral structures can influence vasomotility, blood pressure, heart rate, respiration, thermal regulation, gastric secretion, food intake, and many other functions of the autonomic system. To illustrate the artificial regulation of autonomic reactions by electrical means, I shall discuss pupillary motility because its mechanisms are relatively simple and easy to control.

The areas that participate in the regulation of pupil size are represented on the surface and in the depth of the brain. Cortical zones which have inhibitory effects upon respiration and upon spontaneous movements also produce pupillary dilatation (mydriasis). In cats, dogs, and monkeys, these areas are situated around the sylvian fissure, orbital cortex, temporal tip, cingulate gyrus, insula, rhinal fissure, and hippocampal gyrus. In the depth of the brain, pupillary dilatation may be evoked by stimulation of the basal telencephalon, hypothalamus, septum, midline group of thalamic nuclei, subthalamus, and a large part of the midbrain (Hodes and Magoun, 1942; Kaada, 1951; Showers and Crosby, 1958). Pupillary constriction (miosis) has a more limited representation, localized mainly around the genu of the corpus callosum (Hodes and Magoun, 1942; Kaada, 1951), thalamus, and hypothalamus (Hess, 1954). According to the region stimulated, pupillary responses will be unilateral or bilateral; if bilateral, each eye may respond synergically or antagonically. Most classical studies were performed under anesthesia and with the brain exposed, but recent investigations have been carried out with the use of awake animals equipped with intracerebral electrodes.

In monkeys (Delgado, 1959), electrical stimulation of

FIG. 1. The diameter of the pupil may be electrically controlled as if it was the diaphragm of a photographic camera. The pictures show normal eyes in a monkey and the dilatation and constriction of the right pupil evoked by stimulation of the hypothalamus. Some of these effects are indefatigable and persist for days as long as stimulation is applied.

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the inferior part of the lateral hypothalamus produced marked ipsilateral miosis, while stimulation of another point situated 6 mm. higher in the same tract evoked ipsilateral mydriasis (fig. 1). The magnitude of the effect was proportional to the electrical intensity employed. Stimulation of the inferior point with 0.8 milliampere (mA) produced slight pupillary constriction which increased progressively as the intensity was augmented to 1.5 mA. At this moment, miosis was maximum, and further increase in stimulation did not modify the effect. If the hypothalamic stimulation was slowly decreased in strength, the ipsilateral pupil gradually returned to its normal size. In these experiments, pupil diameter could be controlled precisely like the diaphragm of a camera, by turning the stimulator dials to the left or right. A similar dose-response relation was seen in the higher hypothalamic point where stimulation produced mydriasis. Implantation of electrodes in points with antagonistic pupillary effect made it possible to introduce an artificial conflict by stimulating both areas simultaneously with separate instruments. Results showed that a dynamic equilibrium could be established at different levels of simultaneous antagonistic excitation. With 1.6 footcandle units of illumination in the laboratory, the initial pupillary diameter of 4 mm. was maintained when the hypothalamic points were stimulated together at similarly increasing intensities up to 4 mA. At any level in this dynamic equilibrium, the pupil constricted if intensity was increased in the inferior or decreased in the higher point. The reverse was also true, and the pupil dilated if stimulation decreased in the inferior or increased in the superior hypothalamic point. To some extent, the effect of excitation of the inferior miotic point could be substituted for a light shone in the eye, illustrating the possibility of algebraic summation of physiological, sensory, and electrical stimuli

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within the brain. These experiments demonstrated that a regulation of an autonomic function like pupillary size can be effectively maintained by direct stimulation of cerebral structures.

For how long would this regulation be effective? Would the brain fatigue? To answer these questions, long-term experiments were designed. Under continuous hypothalamic excitation, mydriasis lasted for about 30–40 minutes, after which stimulation was ineffective and the pupil gradually returned to its original size, indicating a slow fatigability of the effect. In contrast, pupillary miosis was maintained in several monkeys for as long as stimulation was applied. Each animal was studied while free in a cage and equipped with a portable stimulator connected by subcutaneous leads to the inferior hypothalamic point. Under continuous 24-hour stimulation, the size of the ipsilateral pupil was maintained at less than 1 mm. in diameter, while the other pupil measured a normal 4 mm. As soon as the stimulation was discontinued, a rebound effect appeared and the ipsilateral pupil dilated to about 6 mm. for several hours, and then slowly returned to its normal size. In one monkey, the stimulation was applied for as long as three days, during which pupil constriction was continuous; with cessation of stimulation, a rebound effect appeared which lasted for two days.

In other experiments, when the intensity of hypothalamic stimulation was adjusted to produce only a 20–30 per cent reduction in pupillary size, the reactivity of both pupils to light was preserved, although the stimulated pupil was always smaller than the control. These results demonstrated that a lasting functional "bias" can be introduced in autonomic reactions by the artificial means of electrical stimulation of the brain. The physiological equilibrium was electrically modified, preserving the responses but changing the

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level of functional adjustment. These results are comparable to the modifications in autonomic reactivity (tuning) induced by injection of sympathetic or parasympathetic agents (Gellhorn, 1957).

In summary, autonomic functions can be controlled by electrical stimulation of the brain. As an example it has been shown that constriction of the pupil evoked by cerebral stimulation is reliable, precise, does not fatigue, can interplay with physiological stimuli, and may provide a functional "bias" to modify the level of physiological responses.

MOTOR PERFORMANCE UNDER ELECTRONIC COMMAND

The significant nineteenth-century discovery of central nervous system excitability was based on the fact that electrical stimulation of the cerebral cortex produced observable motor responses. Since that discovery, many investigations have been devoted to the analysis of motor representation in different areas of the brain. The evoked effects were usually described as stereotyped tetanic contractions, producing clumsy movements of the body and extremities and lacking the precision and coordination of spontaneous activities. These results were obtained under anesthesia, but it was assumed that because of the complexity of the mechanisms involved, artificial stimulation could never induce, even in awake animals, responses as skillful and well organized as voluntary movements. In spite of this assumption, when stimulation was applied through intracerebral electrodes to completely unrestrained animals, it was evident that motor performance under electronic command could be as complex and precise as spontaneous behavior. Before discussing the reasons for success in the electric driving of behavior, I will describe examples of simple motor responses, complex behavior, and social interaction.
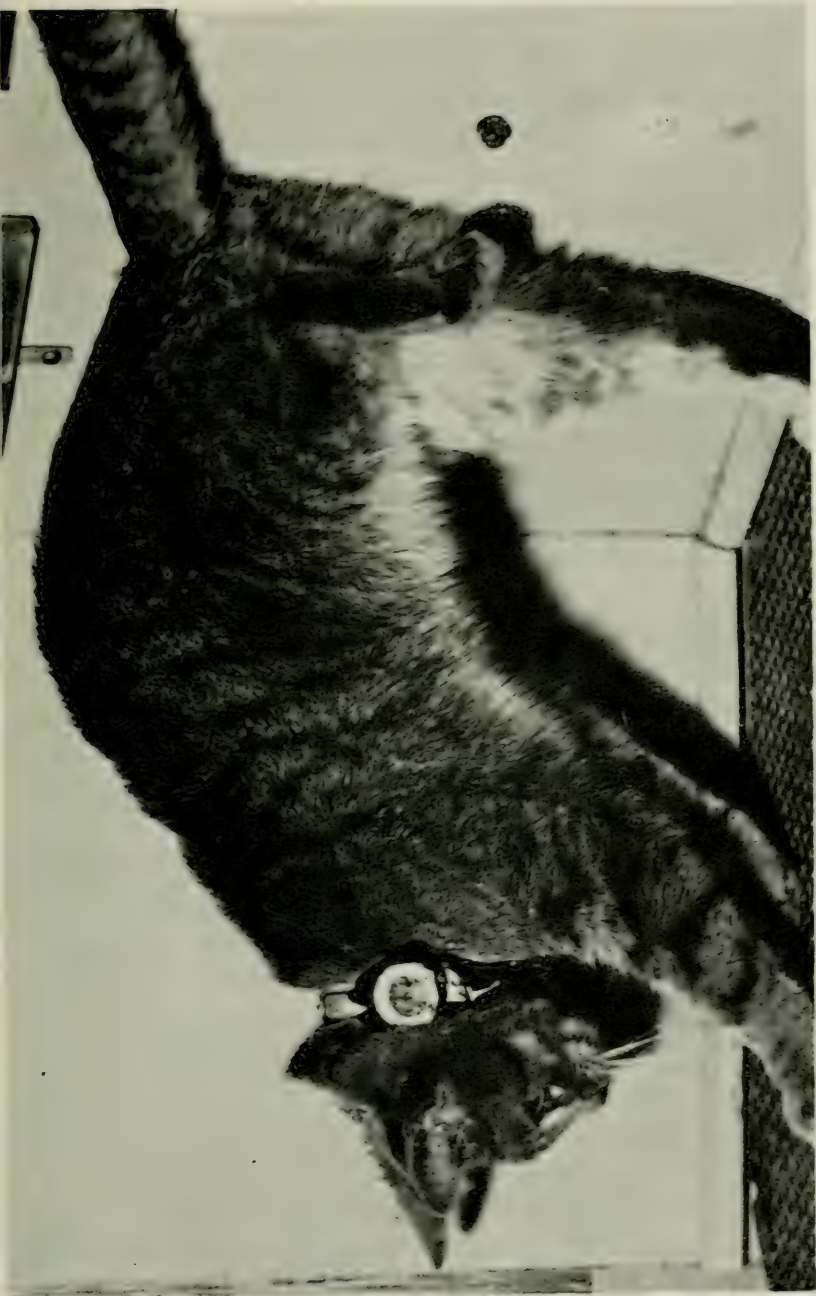
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FIG. 2. Flexions of the left hind leg induced in a cat by electrical stimulation of the cruciate sulcus. This evoked effect is not unpleasant for the animal and may interact with spontaneous activities. Observe the good postural adaptations and the peaceful attitude of the cat.

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In the cat, electrical stimulation of the right sulcus cruciatus, in the anterior part of the brain, produced flexion of the left hind leg (fig. 2) with an amplitude of movement proportional to stimulation intensity, provided the experimental situation was constant. For example, in a cat standing on all fours, a five-second stimulation of 1.2 mA (monopolar, cathodal, square waves, 0.5 millisecond of pulse duration, 100 cycles per second) evoked a leg flexion barely off the ground. When the intensity was increased up to 1.5 mA, the hind leg rose about 4 centimeters, and when 1.8 mA were applied, the flexion of the leg was complete. The evoked movement usually began slowly, developed smoothly, reached its peak in about two seconds, and lasted until the end of the stimulation. This motor performance could be repeated as many times as desired, and it was accompanied by a postural adjustment of the whole body which included a lowering of the head, raising of the pelvis, and a slight weight shift to the left in order to maintain equilibrium on only three legs. The electrical stimulation did not produce any emotional disturbance, and the cat was as alert and friendly as usual, rubbing its head against the experimenter, seeking to be petted, and purring. However, if we tried to prevent the evoked effect by holding the left hind leg with our hands, the cat stopped purring, struggled to get free, and shook its leg. Apparently the evoked motility was not unpleasant, but attempts to prevent it were disturbing for the animal. The artificial driving of motor activities was accepted in such a natural way by the animal that often there was spontaneous initiative to cooperate with the electrical command. For example, during a moment of precarious balance when all paws were close together, stimulation produced first a postural adjustment, and the cat spread its forelegs to achieve equilibrium by

shifting its body weight to the right, and only after this delay did the left hind leg begin to flex. It was evident that the animal was not in a hurry and was taking its time to prepare its position for the induced movement. Preliminary adjustments were not seen if the cat's posture was already adequate for the required motor performance. In other cases, when the animal was lying down with its hind legs already flexed, the stimulation effect was greatly diminished and consisted mainly of increased muscular tension.

In cases of conflict between the free movements of the animal and those elicited by the experimenter, the final result depended on the relative strength of opposing signals. Stimulations of the cruciate sulcus at threshold level of 1.2 mA, which produced a small leg flexion, were ineffective if applied while the cat was walking. To test stronger conflicts, the cat was enticed into jumping off a table to reach food placed on the floor, and, while it was in the air, the cruciate sulcus was electrically stimulated. In this situation, intensities of up to 1.5 mA, which usually evoked a clear motor response, were completely ineffective; physiological activity seemed to override the artificial excitation and the cat landed with perfectly coordinated movements. If the intensity was increased to 2 mA, stimulation effects were prepotent over voluntary activities; leg flexion started during the jump, coordination was disrupted, and the cat landed badly.

A variety of motor effects have been evoked in different species, including cat, dog, bull, and monkey. The animals could be induced to move the legs, raise or lower the body, open or close the mouth, walk or lie still, turn around, and perform a variety of responses with predictable reliability, as if they were electronic toys under human control (see figs. 1–6). Behavior elicited by electrical stimulation was not always comparable to spontaneous activity. In a few

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experiments, movements beyond the animal's voluntary control were observed, such as the clockwise rotation of the eye. In other cases, abnormal responses, disorganized contractions, and loss of equilibrium have also been induced, depending on the cerebral area and parameters of stimulation.

COMPLEX BEHAVIOR

Normal activities in animals are not confined to simple motor responses such as hind-leg flexion but include a succession of different acts such as body displacement and social interaction. In order to study these complex activities, which require a situation as free and normal as possible, our experimental design included (1) the establishment of a colony with four to six monkeys, (2) the continuous recording of spontaneous and evoked behavior by time-lapse photography, in order to qualify and quantify individual and social actions, and (3) stimulation of the animals by remote control. The behavior of a group of monkeys is an entertaining spectacle, and a few minutes' observation gives the impression that their playing, grooming, chasing, and comic activities are rather unpredictable. Long-term studies, however, have shown that individual and social behavior is predictable within a known range of variability. The study of group behavior is possible precisely because of the recurrence of patterns that can be identified. Every day the monkeys will eat, play, groom, pick, sit, and perform a series of acts which can be analyzed and quantified (Delgado, 1962). After the individual profiles of behavior are established, the responses evoked by electrical stimulation of the brain may be precisely evaluated.

A typical example of complex behavior was observed in a monkey named Ludi while she was forming part of a

Fig. 3. Yawning evoked in the monkey by radio stimulation of the pars magno cellularis of the red nucleus. Observe the spontaneous qualities of the evoked effect and also the fact that when the monkey is asleep the response diminishes.

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colony with two other females and two males. Ludi was an aggressive female who dominated the whole group and exercised the usual prerogatives of being the chief, enjoying greater territoriality and more food, and moving freely around the colony. After different areas of the brain had been studied under restraint, the radio stimulator was strapped to Ludi, and excitations of the rostral part of the red nucleus were started, with the monkey free in her colony. Stimulation produced the following complex sequence of responses (fig. 4): (1) immediate interruption of spontaneous activities, (2) change in facial expression, (3) head turning to the right, (4) standing on two feet, (5) circling to the right, (6) walking on two feet with perfect preservation of equilibrium by balancing the arms, touching the walls of the cage, or grasping the swings, (7) climbing a pole on the back wall of the cage, (8) descending to the floor, (9) low tone vocalization, (10) threatening attitude directed toward subordinate monkeys, (11) changing of attitude and peacefully approaching some other members of the colony, and (12) resumption of the activity interrupted by the stimulation. The whole sequence was repeated again and again, as many times as the red nucleus was stimulated. Responses 1 to 8 developed during the five seconds of stimulation and were followed, as aftereffects, by responses 9 to 12 which lasted from five to 10 seconds. The excitations were repeated every minute for one hour, and results were highly consistent on different days. The responses resembled spontaneous activities, were well organized, and always maintained the described sequence. Climbing followed but never preceded turning of the body; vocalization followed but never preceded walking on two feet; the general pattern was similar in different stimulations, but the details of motor performance varied and were adjusted to existing circumstances. For example, if the stimulation
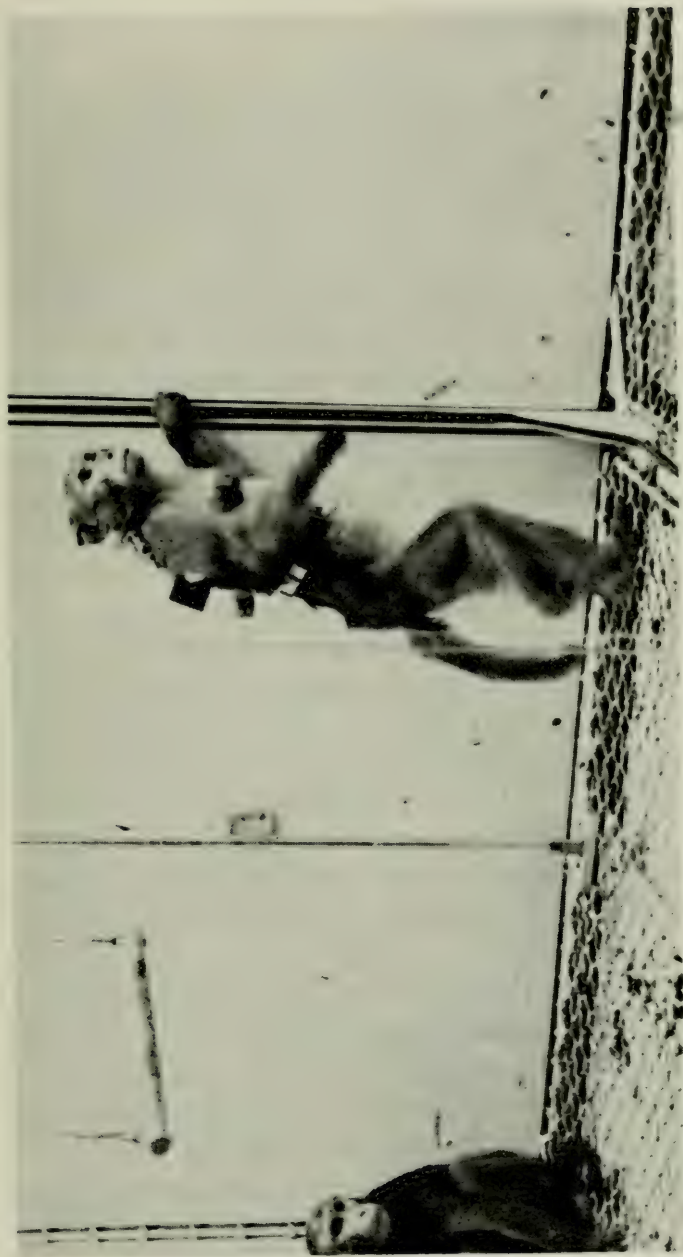
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FIG. 4. As mentioned in the text, a sequence of effects including walking on two feet may be evoked by radiostimulation of the red nucleus.

surprised the animal with one arm around the vertical pole in the cage, the first part of the evoked response was to withdraw the arm in order to make the turn possible. While walking on two feet, the monkey was well oriented and was able to avoid obstacles in its path and to react according to the social situation. In some experiments, three monkeys in the colony were simultaneously radio-stimulated in the red nucleus, and all three performed the full behavioral sequence without interfering with one another. Changes in the experimental situation could modify the evoked response, as shown in the case of external threat to the colony. Waving the catching net or a pair of leather gloves on one side of the home cage induced a precipitous escape of all monkeys to the other side. Red-nucleus stimulation applied at this moment was ineffective and did not interfere with the escape of the animals. In other experiments, after being deprived of food for 24 hours, the animals were offered bananas and oranges which they grabbed and ate voraciously. During this time, Ludi's response to radio stimulation of the red nucleus was completely absent or was reduced to only a short turn. In one long experiment, excitation of the red nucleus was repeated every minute, day and night, for two weeks, with a total of more than 20,000 stimulations. The remarkable reliability of responses was demonstrated throughout the whole period, with the following significant exception. During the day, monkeys take several naps, and during the night they have a long period of sleep which is interrupted by several periods of general activity. Time-lapse recordings showed that, as the stimulated monkey was falling asleep, the evoked responses progressively diminished until only a small head movement remained. As soon as the stimulated animal awoke, the responses reappeared with all of their complexity. This finding indicates that the effects evoked by cerebral stimulation are not inflexible and

rigid, but may adapt to changes in the physiological situation. Examples of other patterns of sequential behavior have been evoked by excitation of several diencephalic and mesencephalic structures (Delgado, 1963a, 1964a, 1964b), showing that sequential activities are anatomically represented in several parts of the central nervous system.

SOCIAL INTERACTION

The social interaction of animals requires continuous mutual adaptation, and activities depend on a variety of factors, including sensory inputs, problem-solving capacity, emotional background, previous experience, conditioning, drives, instincts, and intelligent integration of all these processes. In spite of the extraordinary complexity of these supporting mechanisms, there is experimental evidence that electrical stimulation of specific areas of the brain may influence social interaction such as contactual relations, hierarchical situations, submissive manifestations, sexual activity, aggressive behavior, and social fear. By definition, this type of research requires at least two animals which can interact with each other, but the study of groups is naturally preferable.

In 1928 Hess demonstrated that during electrical stimulation of the periventricular gray matter, cats responded as if threatened by a dog, with dilatation of the pupils, flattening of the ears, piloerection, growling, and well-directed blows with unsheathed claws. Similar offensive-defensive reactions have been described by several authors (see bibliography in Delgado, 1964a), but it was debatable whether the apparently enraged animal was aware of its own behavior and whether the evoked reactions were purposefully oriented; in other words, if the observed phenomena were true or false rage. Today it is known that both types of rage may be elicited, depending on the loca-

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tion of the stimulated points, and we have conclusive evidence that, in cats and monkeys, well-organized behavior may be evoked by stimulation of the amygdala, posteroventral nucleus of the thalamus, fimbria of the fornix, tectal area, central gray, and other cerebral structures. The fact that one animal can be electrically driven to fight against another has been established (Delgado, 1955a). In this experiment, stimulation of the tectal area in a male cat evoked the well-known pattern of offensive-defensive reactions. When this animal was placed on a testing stage in the company of a larger cat, they enjoyed friendly relations, lying close to each other and purring happily until the smaller cat was stimulated in the tectal area. At this moment, it started growling, unsheathed its claws, and launched a fierce attack against the larger animal which flattened its ears, withdrew a few steps, and retaliated with powerful blows. The fight continued as long as the stimulation was applied. The effect could be repeated, and the stimulated cat always took the initiative in spite of the fact that it was smaller and was always overpowered in the battle. After several stimulations, a state of mistrust was created between the two animals, and they watched each other with hostility.

Similar experiments were repeated later in a colony formed by six cats. When one of them was radio-stimulated in the tectal area, it started prowling around looking for fights with the other subordinate animals, but avoiding one of them which was the most powerful of the group. It was evident that brain stimulation had created a state of increased aggressiveness, but it was also clear that the cat directed its hostility intelligently, choosing the enemy and the moment of attack, changing tactics and adapting its motions to the motor reaction of the attacked animal. In this case, brain stimulation seemed to determine the affec-

tive state of hostility, but the behavioral performance seemed dependent on the individuality of the stimulated animal, including its learned skills and previous experiences. Stimulation that increased aggressiveness was usually tested for only five to 10 seconds, but, as it was important to determine the fatigability of the effect, a longer experiment was performed by reducing the intensity to a level which did not evoke overt rage. The experimental subject was an affectionate cat which usually sought petting and purred while it was held in the experimenter's arms. When it was introduced into the colony with five other cats, a low-intensity radio stimulation of the amygdala was applied continuously for two hours during which the animal's behavior was affected. It withdrew to a corner of the cage and sat there motionless, uttering barely audible growls from time to time. If any other cat approached, the stimulated animal started hissing and threatening, and, if the experimenter tried to pet him, the growls increased in intensity and the animal often spat and hissed. This hostile attitude disappeared as soon as the stimulation was over, and the cat became as friendly as before. These experiments demonstrated that brain stimulation could modify animals' reactions toward normal sensory perceptions by a modulating of the quality of the responses. The effect was similar to the modifications of spontaneous behavior observed in normal emotional states.

Monkeys offer better opportunities than cats for the study of social interaction because of their more numerous and skillful spontaneous activities. It is well known that these animals form autocratic societies, where one establishes himself as boss of the group, claiming a large amount of the living quarters as his territory, feeding first, and being avoided by the others, which usually express their submissiveness by typical actions such as grimacing,

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crouching, and presenting. In several of our monkey colonies, we demonstrated that radio stimulation of the posteroventral nucleus of the thalamus and central gray increased the aggressiveness of the stimulated animal and affected the social hierarchy. Stimulation of the boss monkey induced well-directed attacks against the other members of the group, which were chased around and occasionally bitten, but it was evident that the orientation of the evoked response was influenced by previous experiences. During stimulation, the boss usually attacked and chased the male monkeys which represented a challenge to his authority, but he did not threaten the female who was his favorite partner. These results confirmed the finding in cat colonies that aggressiveness induced by cerebral stimulations was not blind and automatic, but selective and intelligently directed.

Rhesus monkeys are destructive and dangerous creatures which do not hesitate to bite anything within reach, including leads, instrumentation, and occasionally the experimenter's hands. Would it be possible to tame these ferocious animals by means of electrical stimulation? To investigate this question, a monkey was strapped to a chair where it made faces and threatened the investigator until the rostral part of the caudate nucleus was electrically stimulated. At this moment, the monkey lost its aggressive expression and did not try to grab or bite the experimenter, who could safely put a finger into its mouth! As soon as stimulation was discontinued, the monkey was as aggressive as before. Later, similar experiments were repeated with the monkeys free inside the colony, and it was evident that their autocratic social structure could be manipulated by radio stimulation. In one case in which the boss monkey was excited in the caudate nucleus with 1.5 mA for five seconds every minute, after several minutes the other mon-
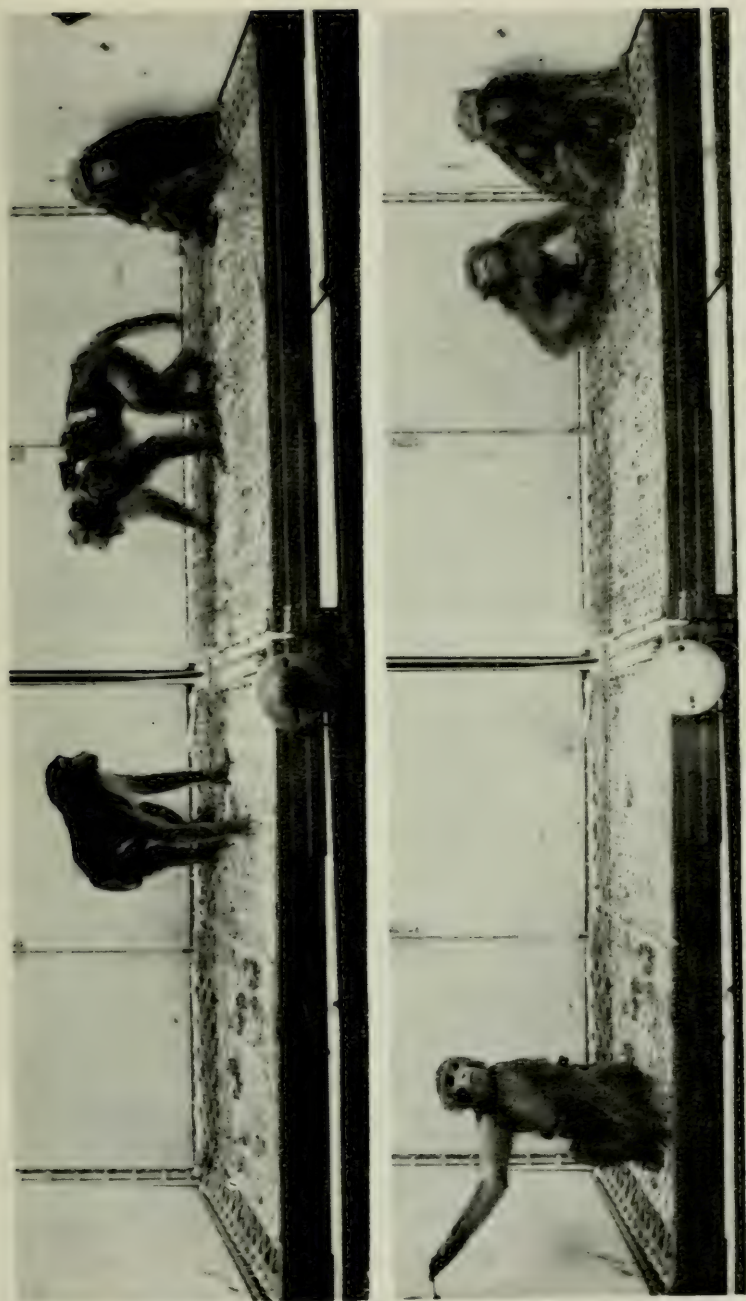
FIG. 5. Monkeys may learn to press a lever in order to stimulate by radio the brain of another aggressive animal and in this way to avoid his attack. Heterostimulation in monkey colonies demonstrates the possibility of instrumental control of social behavior.

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keys started to circulate more freely around the cage, often in proximity to the boss, and from time to time they crowded him without fear. The intermittent stimulation continued for one hour, and during this time the territoriality of the boss dropped to zero, his walking time was diminished, and he performed no aggressive acts against the other members of the colony. About 12 minutes after the stimulation hour ended, the boss had reasserted his authority, and his territoriality seemed to be as well established as during the control period. In other experiments, monkeys instead of investigators controlled the activation of radio stimulation. In this situation, subordinate animals learned to press a lever in the cage which triggered stimulation of the boss monkey in the caudate nucleus, inhibiting his aggressive behavior (fig. 5; Delgado, 1963c). Inhibitory effects have been demonstrated in several species including brave bulls, as shown in figure 6 (Delgado, *et al.,* 1964).

A different type of effect was demonstrated in another monkey colony. Radio stimulation of the nucleus medialis dorsalis of the thalamus in a female monkey produced a sequential pattern of behavior characterized by a movement of the head, walking on all fours, jumping to the back wall of the cage for two or three seconds, jumping down to the floor, and walking back to the starting point. At this moment, she was approached by the boss of the colony and she stood on all fours, raised her tail and was grasped and mounted by the boss in a manner indistinguishable from spontaneous mounting. The entire behavioral sequence was repeated once every minute following each stimulation, and a total of 81 mountings was recorded in a 90-minute period, while no other mountings were recorded on the same day. As is natural in social interaction, the evoked responses affected not only the animal with cerebral electrodes, but also other members of the colony.

FIG. 6. A bull in full charge may be suddenly stopped by radio stimulation of the anterior part of the thalamus.

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The experimental evidence presented in the previous pages clearly demonstrates that electrical stimulation of the brain can induce predictable behavioral performance similar to spontaneous activities. Understanding the significance of these findings requires analysis of the physiological mechanisms involved in voluntary movements. A simple act such as leg flexion requires the precise and progressive contraction of several muscles in which the strength, speed, and amplitude of activation of many motor units are determined by the processing of messages coming from joints and muscle spindles integrated with another vast amount of information circulating through the central nervous system. The complexity of neuronal events is even greater during performance of sequential responses, in which timing and motor correlations must be adjusted to the purpose of the movement and adapted to changes in the environment. Mechanisms responsible for the physiological excitation of spontaneous motility must be highly sophisticated. In contrast, electrical stimulation of the brain is very simple and depends on primitive techniques that apply a train of pulses without modulation, without code, without specific meaning, and without feedback to a group of neurons which by chance are situated within an artificially created field. In view of the complexity of neuronal integrations, it is not surprising that a few authors have downgraded the significance of stimulation effects. How can we explain the contradiction between the crudeness of these excitations and the refinement of the responses that they can elicit?

When considering whether a simple electrical stimulus could be the cause of the many events of a behavioral response, we could ask whether a finger pushing a button to launch a man into orbit is responsible for the complicated

machinery or for the sequence of operations. Evidently the finger, like a simple stimulus, is only the trigger of a programmed series of events, and consequently electrical charges applied to the brain cannot be accepted as the direct cause of leg flexion or aggression. The effect of electricity is simply to depolarize some neural membranes and to initiate a chain reaction. We must remember that even at the neuronal level, electrical excitation is not responsible for the many biochemical, enzymatic, thermal, and electrical processes which accompany the evoked action potentials. Evoked effects, like other chain reactions, depend more on the functional properties of the activated structures than on the starter. If electrical stimulation is considered as a non-specific trigger, our discussion must be focused on *what* is triggered. Why do movements start, develop, and end? Which motor mechanisms are involved within the brain? These basic neurophysiological questions are very difficult to answer because of our limited knowledge, but at least we now have some new tools to initiate their study, and experimental hypotheses to guide future research.

A tentative explanation of some of the mechanisms involved in motor activities has been proposed in the theory of fragmental representation of behavior (Delgado, 1964a) which postulates that behavior is organized as fragments which have anatomical and functional reality within the brain, where they can be the subject of experimental analysis. The different fragments may be combined in different sequences like the notes of a melody, resulting in a succession of motor acts which constitute specific behavioral categories such as licking, climbing, or walking. The theory may perhaps be clarified with one example. If I wish to take a cookie from the table, this wish may be considered as a force called *the starter* because it will determine the initia-

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tion of a series of motor acts. The starter includes drives, motivations, emotional perceptions, memories, and other processes. To take the cookie it is necessary to organize a motor plan, a mechanical strategy, and to decide among several motor choices, because the cookie may be taken with the left or right hand, directly with the mouth, or even by using the feet if one has simian skills. Choice, strategies, motor planning, and adjustments depend on a set of cerebral structures, *the organizer,* which is different from the set employed by the starter, because the desire for cookies may exist in hungry people or in completely paralyzed patients, and the hands can move and reach the table for many different reasons even if there are no cookies. Finally, the actual contraction of muscles for the performance of the selected movement to reach the cookie—for example, using the right hand—depends on a cerebral set, *the performer,* different from the previous two, because motor representation of hands, mouth, and feet is situated in different areas of the brain, and the choice of muscle group to be activated is under the supervision of a given organizer. Naturally, there is a close correlation among these three basic mechanisms, and also between them and other cerebral functions. The concept of a brain center as a visible anatomical locus is unacceptable in modern physiology, but the participation of a constellation of neuronal groups (a functional set) in a specific act is more in agreement with our present knowledge. The functional set may be formed by the neurons of nuclei far from one another: for instance, in the cerebellum, motor cortex, pallidum, thalamus, and red nucleus, forming a circuit in close mutual dependence, and responsible for a determined act such as picking up a cookie with the right hand.

If we accept the existence of anatomical representation of the three functional sets: starter, organizer, and per-

former, it is logical that they can be activated by different types of triggers, and that the evoked results will be related to the previous experiences linked to the set. The same set, evoking a similar behavioral response, may be activated by physiological stimuli, such as sensory perceptions and ideations, or by artificial stimuli, such as electrical impulses. Depending on the location of contacts, when we stimulate the brain through implanted electrodes we can activate the starter, the organizer, or the performer of different behavioral reactions, so that natural and artificial stimuli may interplay with one another, as has been experimentally demonstrated.

These theoretical considerations may facilitate the understanding of so-called willful, free, or spontaneous activity. Obviously, the will is not responsible for the chemistry of muscle contraction, for the electrical processes of neural transmission, or even for the intimate organization of movements; these phenomena depend on spindle discharges, cerebellar activation, synaptic junctions, reciprocal inhibitions, and other subconscious mechanisms. Voluntary activity is initiated by a physiological trigger which activates a chain of preformed mechanisms which exist independently inside the brain. The uniqueness of voluntary behavior lies in its wealth of starters, each one of which depends on a vast and unknown integration of past experiences and present receptions. However, the organizers and performers are probably activated in a similar manner by the will and by electrical means, providing the possibility of investigating experimentally some of the basic mechanisms of spontaneous behavior.

One limitation of electrical activation of behavior is the anatomical variability of the brain. Just as there are external physical differences between individuals, there are variations in the shape and size of our cerebral structures

which make it impossible to place an electrical contact in exactly the same location in different subjects. Another important limitation is functional variability. The organization of brain physiology depends to a great extent on individual experience which determines the establishment of many temporary or permanent associations among neuronal fields. For example, the sound of a bell is neutral for a naive animal, but will induce secretion of saliva if it has previously been paired with food, and stimulation of the auditory cortex should increase salivary secretion only in the conditioned animal. Anatomical and functional variabilities are the bases for the differences in individual personalities. When we stimulate the motor cortex, we can predict the appearance of a movement but not the details of its performance, indicating that the effects elicited by electrical stimulation of the brain have a statistical but not an individual determination.

ELECTRICAL DRIVING OF
MENTAL FUNCTIONS IN MAN

Elemental psychic phenomena such as hunger and fear can be analyzed in both animal and man, but processes like ideation and imagery that are expressed verbally can be studied only in human beings. The most extensive information on this subject has been obtained by Penfield and his group (see, for instance, Penfield and Jasper, 1954) during surgical operations for epilepsy, tumors, or other illnesses. In these procedures, the brain was exposed under local anesthesia and stimulated electrically under direct visual control. More recently, as explained in a previous section, electrodes have been implanted in the brain for days or weeks, permitting repeated studies in a relaxed atmosphere, with the patient in bed or sitting comfortably in a chair. From Penfield's publications and from implanted-

electrode studies, a considerable amount of information has demonstrated that brain stimulation may induce anxiety, fear, hostility, pleasure, feelings of loneliness, distortion of sensory perception, recollection of the past, hallucinations, and other psychic manifestations. From all this material, I shall select several representative examples dealing mainly with ideation, which is perhaps the most interesting and least understood of the mental processes.

SPEECH INCREASE

Patient A. F. was an 11-year old boy committed to an institution because of his uncontrollable epileptic seizures and destructive behavior (see Higgins *et al.*, 1956). Since his response to drugs and treatment was unsatisfactory, brain surgery was decided upon. To direct the operation, four electrode assemblies were implanted in the temporal lobes for six days. During this time, intracerebral activity was recorded, and several spontaneous seizures were registered. Exploration of the patient included several tape-recorded interviews of from one and a half to two hours, behavioral observations, and 69 intracerebral stimulations. Study of the collected data indicated the existence of a focus of abnormality in the left temporal tip, and this area was successfully removed. Recovery from surgery was un-eventful, and in a few weeks the boy was able to enjoy a normal life and return to school. Five years later he was still seizure-free.

In our investigations, the conversations between patient and therapist were tape-recorded while the spontaneous electrical activity of the brain was also being registered, and programmed stimulations were applied to different cerebral points. The general procedure was explained to the patient, but, to avoid possible psychological influences, he was not informed of the exact moment of the stimula-

tions. To establish behavioral and electrical correlations, the recorded interviews were transcribed, divided into periods of two minutes, and analyzed by two independent investigators who counted the number of words and identified and quantified the verbal expressions according to 39 different categories. Table 1 shows the stimulation effects on verbal production. During this interview, the patient was quiet and spoke only four to 17 words every two minutes. Whenever point RP 1–2 was stimulated, the patient's attitude changed; he became more animated, and his verbal output increased sharply to a mean of 88 words per two-minute period.

TABLE 1
(From Higgins, Mahl, Delgado, and Hamlin, 1956)

Stimulations Time interval	RP 1-2 (N-7) 2'Postim.	2'Prestim.	t-Test P-Value	All Others Stimulations (N-7) 2'Postim.	2'Prestim.	t-Test P-Value
Mean % friendly remarks	6	53	0.02	17	10	—[a]
Mean N words by patient	17	88	<0.01	4	9	0.15
Mean N words by Int.	43	46	—[a]	16	30	>0.30

[a]Insignificant by inspection.

These effects were repeated seven times, and in each stimulation the patient appeared to be especially optimistic, emphasizing the pleasant side of sensory perceptions and the happy aspects of his memories and ideas, with many of his comments affectionately directed and personally related to the therapist. Verbal expression was spontaneous in character, his usual personal style and phraseology were preserved, and conversational topics were related to the experimental situation without a preferred theme. Table 1 shows that the evoked increase of words and of friendly remarks were highly significant, as evaluated by the t-test, and also that the effect was specific because it was not produced by stimulation of other cerebral points.

In three different patients, thoughts and expressions with sexual content were induced by electrical stimulation of the temporal lobe. The first case, S. S., was an intelligent and attractive woman, 32 years old, who had suffered from uncontrollable epileptic attacks for several years. During the interviews she was usually reserved, but the first time that point A in the second temporal convulsion was excited with 6 volts, she became visibily affected, holding the hands of the therapist to express her fondness for him and to thank him for all his efforts. Several minutes later, after another stimulation of the same point, she started to say how much she would like to be cured so that she might marry, and other stimulations of point A were also followed by flirtatious conversation. The provocative play and ideas expressed under stimulation of point A did not appear following stimulation of other cerebral points and contrasted with this woman's usually reserved spontaneous behavior.

The second patient, V. P., was a woman 36 years old who had suffered from epilepsy since childhood. Point C in the temporal lobe was excited five times at intervals of from five to 10 minutes, and after each stimulation the patient's mood became friendlier; she smiled, questioned the therapist directly about his nationality, background, and friends, and declared that he "was nice," that his country (Spain) "must be very beautiful," that "Spaniards are very attractive," and she ended with the statement "I would like to marry a Spaniard." This particular train of thought and manner of speaking seemed completely spontaneous, but it appeared only after stimulation of point C in the temporal lobe, and no such shift to a flirtatious mood was noted in her spontaneous conversations following stimulations of other cerebral points.

The third case of evoked change in sexual ideology was

a young epileptic boy, A. F., who, following stimulation of point LP 5–6 in the left temporal cortex, suddenly began to discuss his desire to get married. After subsequent stimulations of the point, he elaborated on this subject, revealed doubts about his sexual identity, and voiced a thinly veiled wish to marry the male interviewer.

Experiential Hallucinations

Hallucinations evoked by electrical stimulation of the brain have been lucidly described by Roberts (1961), who wrote: "It is as though a wire recorder, or a strip of cinematographic film with sound track, had been set in motion within the brain. A previous experience—its sights and sounds and the thoughts—seems to pass through the mind of the patient on the operating table. . . . At the same time he is conscious of the present. . . . The recollection of the experiential sequence stops suddenly when the electric current ceases. But it can again be activated with reapplication of the electric current." The hallucination may develop during the stimulation, with a normal-like progression of movements and sounds, which appear more real and vivid than when the events actually happened. It is as if the patient had a double life, one in the past recalled by the electrical stimulation, and another in the present, perceiving all the sensory stimulation of the surroundings, but both with a similar quality of reality, as if the person had a "double consciousness" of subjective sensations. In some cases, components of the hallucination are completely new and do not belong to the subject's past experience, but usually, as Penfield (1952, 1958, 1960) emphasized, the responses are a detailed reenactment of previous experiences, an exact "flash-back" activation of memories.

In one of our patients with intracerebral electrodes, detailed study of the tape-recorded interviews demonstrated that the perceptual content of some experiential responses

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was related to the patient's thoughts at the moment of stimulation. For example, when the patient was talking about her daughter's desire for a baby sister, a stimulation was applied to the temporal lobe and the patient heard a female voice saying "I got a baby—sister." Baldwin (1960) has reported a similar observation in which the content of visual hallucinatory responses evoked in a 28-year old man varied with the sex and identity of the observer seated before him in the operating room. In a previous article (Mahl et al., 1964) we have suggested that "The patient's 'mental content' at the time of stimulation is a determinant of the content of the resulting hallucinatory experiences," and we offered the so-called "altered-state hypothesis" in which the essential effect of stimulation is to alter the state of consciousness of the patient in such a way that primary process thinking replaces secondary process thinking. (See Freud, 1900.) According to this hypothesis, the electrical stimulation of the temporal lobe would not activate memory traces in the ganglionic record, as postulated by Penfield, but would induce a state of consciousness which would increase the functional probability of primary processes.

Pleasure

The possibility that "pleasure centers" might exist in the brain was supported by the extensive work of Olds and his collaborators (1954, 1956, 1961), who demonstrated that rats prefer to stimulate some points of their brains by pressing a treadle, than to satisfy drives of hunger, thirst, and sex. Positive behavioral qualities of cerebral stimulation have been confirmed in other species including the cat (Sidman et al., 1955) and the monkey (Bursten and Delgado, 1958). However, "pleasure" has an experiential factor which animals cannot report because they lack verbal communication. Only studies in humans could reveal whether

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electrical stimulation of the brain is able to induce pleasurable sensations. The study of patients with implanted electrodes yielded affirmative evidence (Delgado, 1960; Sem-Jacobsen and Torkildsen, 1960). In one of our cases, stimulation of the temporal lobe evoked "pleasant tingling sensations of the body" which were openly declared to be very enjoyable. The patient's mood changed from its usual peaceful state to one of giggling and laughing. She teased the doctor and made fun of the experimental situation with humorous comments.

In another patient, temporal-lobe stimulation evoked "statements avowing his pleasure at being 'up here' and 'subject to us' which were classified as 'passive compliance' " (Higgins *et al.*, 1956). For example, when the patient had been silent for five minutes, a point in the temporal cortex was stimulated and he immediately exclaimed, "Hey! You can keep me longer here when you give me these; I like those." and he insisted that the "brain wave" testing made him "feel O.K." Similar statements followed stimulation of other temporal points, but were never expressed spontaneously in the absence of excitations. The statistical significance of these results was P < 0.001, as contrasted by X^2 analysis.

During increased pleasure, the subjects were oriented mainly toward themselves, and they often reported experiencing agreeable physical sensations, while during artificially increased speech and changes in sexual ideology they expressed friendliness for the nearby people. In both cases, there was a shift of emotional mood to a happy interpretation of reality, and this experience was interpreted by the patient as spontaneous and valid, usually without being directly related to the stimulation. A shift from pleasurable thinking to friendliness and to sexual ideas has been observed in some cases.

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Probably the most significant conclusion derived from electrical stimulation of the awake brain is that functions traditionally related to the psyche such as friendliness, pleasure, and verbal expression can be induced, modified, and inhibited by direct stimulation of cerebral structures. This discovery may be compared with the revolutionary finding almost two centuries ago that contraction of frog muscle may be induced by electricity without need of the soul's "animal spirits," because experimental analysis of mental functions can now proceed without implicating metaphysical entities. Research concerning the electrical driving of emotions, anatomical correlates of memory, or electrical signals related to learning does not interfere with personal ideas about the natural or supernatural destiny of man and does not involve theological questions, which should be disassociated from neurophysiological inquiry. In addition to electrical stimulation, there are now techniques for exploration of brain function which include electrical recording, chemical stimulation, intracerebral chemistry, and electron microscopy. The task that we are facing is the correlation of neuro-anatomy and physiology with mental functions; the investigation of cerebral areas involved in psychic manifestations; the analysis of their electrical and chemical background; and the development of methods to induce or inhibit specific activities of the mind.

Already we know that some structures, including the hypothalamus, amygdala, central gray, and temporal lobe, are involved in emotional phenomena, while other areas, such as the parietal cortex, do not seem to participate in psychic experience. Brain research has expanded rapidly in recent years with the creation of institutes for multi-disciplinary studies, but this field should attract even more of our intellectual and economic resources. Human behav-

ior, happiness, good, and evil are, after all, products of cerebral physiology. In my opinion, it is necessary to shift the center of scientific research from the study and control of natural elements to the analysis and patterning of mental activities. There is a sense of urgency in this redirection because the most important problem of our present age is the reorganization of man's social relations. While the mind of future generations will be formed by pedagogic, cultural, political, and philosophical factors, it is also true that education is based on the transmission of behavioral, emotional, and intellectual patterns related to still unknown neurophysiological mechanisms. Investigators will not be able to prevent the clash of conflicting desires or ideologies, but they can discover the neuronal mechanisms of anger, hate, aggressiveness, or territoriality, providing clues for the direction of emotions and for the education of more sociable and less cruel human beings. The precarious race between intelligent brains and unchained atoms must be won if the human race is going to survive, and learning the biological mechanisms of social relations will favor the cerebral victory.

Electrical and chemical analyses of mental functions have introduced new facts into the much debated problem of mind-brain relations. In the interpretation of data, we should remember that spike potentials, neurohumors, and synaptic transmitters may represent happiness and sorrow, love and hate, war and peace, and in the near future we can expect to find answers to classical questions concerning psychological aspects of the physical brain. How can electrical stimulation of the temporal lobe be felt as pleasure, music, or fear? Why is a ferocious monkey tamed by applying a few volts of electricity to its caudate nucleus? As discussed in a previous article (Delgado, 1964b), psychophysical correlations may be related to the two elements

which transmit information in the nervous system, namely, the *material carrier* and the *symbolic meaning*. In the reception of sensory inputs, there is an initial *electrical coding* which is the carrier necessary for neural circulation of impulses. When a monkey, a savage, or a civilized man looks at a pencil, the received visual stimulus is transformed into electrical signals and transmitted through optic pathways to the brain. At the levels of retina and optic nerve, the coding of the stimulus depends on the visual input, independent of its possible meaning. Symbolism is created by the association within the brain of two or more sensory receptions or of present and past experiences, but it does not depend on the material structure of the object or on the pattern of its electrical coding. For a naive monkey or for a savage, the pencil is a neutral object; for a writer, the pencil is full of associations, uses, and meaning. Symbolism is not intrinsic in the object, nor inborn in the brain: it must be learned. The most important symbolic tool of the mind, language, is not invented by each individual; it is a cultural gift of the species. The symbolic meaning may be considered an *immaterial element of mental functions* in the sense that it is related to a spatio-temporal association between two or more sensory receptions and not to the material structure of the inputs. The elements for symbolic recognition already exist in the electrical code of the transmitted signals; however, they are not determined by the pattern of the code but by spatio-temporal relations between present and past codes which cannot be deciphered by any instrument if the reference point of the past is not known. These temporal and spatial relations may be considered as material or immaterial, depending on the investigator's point of view. Obviously, the relations depend on the material existence of some events, but, at the same time, the relations are independent of the material organization of

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each event. It is a question of definition, and, if we explain the meaning of our terms, there is no conflict. I think, however, that it is more practical to consider symbolism as *non* material in order to emphasize the relativity of its existence and the fact that it does not depend on the intrinsic qualities of matter but on the previous history of the object and of the observer. In the last analysis, behavior could be reduced to movement of atoms, but if we are discussing the emotional behavior of the monkey, it would be difficult to explain it in terms of orbiting particles, and it is far more useful to employ psychological concepts. It should be clarified that, in the observer, conscious understanding of meaning is probably dependent upon progressive steps of electrical subcoding of sensory inputs with the creation of new material and symbolic elements related to the activation of a new series of chemical and electrical phenomena affecting specialized neurons. However, the distinction between material carrier and symbolic meaning simplifies the interpretation of neurophysiological data, because analysis of events in receptors and in transmitting pathways will provide information about the carrier but not about symbols. At the same time, it should be expected that electrical stimulation of neuronal groups may activate processes related to both material carriers and symbolic meaning. This working hypothesis may help in the differentiation between cerebral mechanisms responsible for transmitting inputs and for cognitive processes of received signals.

From its beginning, wiring of the human brain aroused emotional opposition even among scientists, while similar wiring of the heart or of the bladder has been received enthusiastically. The difference in attitude was no doubt related to a more or less conscious personal fear that our identity could be attacked and that our mind could be controlled. Personal traits such as friendliness, sexual in-

clination, or hostility have already been modified during cerebral stimulation, and we can foresee other influences on emotional tone and behavioral reactions. Electricity is only a trigger of pre-existing mechanisms which could not, for example, teach a person to speak Spanish, although it could arouse memories expressed in Spanish if they were already stored in the brain.

Entering into the field of speculation, I would like to comment on one question which has already caused widespread concern. Would it be feasible to control the behavior of a population by electrical stimulation of the brain? From the times of slavery and galleys up to the present forced-labor camps, man has certainly tried to control the behavior of other human beings. In civilized life, the intervention of governments in our private biology has become so deeply rooted that in general we are not aware of it. Many countries, including the United States, do not allow a bride and groom to marry until blood has been drawn from their veins to prove the absence of syphilis. To cross international borders, it is necessary to certify that a scarification has been made on the skin and inoculated with smallpox. In many cities, the drinking water contains fluoride to strengthen our teeth, and table salt is fortified with iodine to prevent thyroid misfunction. These intrusions into our private blood, teeth, and glands are accepted, practised, and enforced. Naturally, they have been legally introduced, are useful for the prevention of illness, and do generally benefit society and individuals, but they have established a precedent of official manipulation of our personal biology, introducing the possibility that governments could try to control general behavior or to increase the happiness of citizens by electrically influencing their brains. Fortunately, this prospect is remote, if not impossible, not only for obvious ethical reasons, but also because of its impracticability.

Theoretically it would be possible to regulate aggressiveness, productivity, or sleep by means of electrodes implanted in the brain, but this technique requires specialized knowledge, refined skills, and a detailed and complex exploration in each individual, because of the existence of anatomical and physiological variability. The feasibility of mass control of behavior by brain stimulation is very unlikely, and the application of intracerebral electrodes in man will probably remain highly individualized and restricted to medical practice. Clinical usefulness of electrode implantation in epilepsy and involuntary movements has already been proved, and its therapeutical extension to behavioral disorders, anxiety, depression, and other illness is at present being explored. The increasing capacity to understand and manipulate mental functions of patients will certainly increase man's ability to influence the behavior of man.

If we discover the cerebral basis of anxiety, pleasure, aggression, and other mental functions, we shall be in a much better position to influence their development and manifestations through electrical stimulation, drugs, surgery, and especially by means of more scientifically programmed education.

These possibilities pose tremendous problems. As Skinner asked recently (1961), "Is the deliberate manipulation of a culture a threat to the very essence of man or, at the other extreme, an unfathomed source of strength for the culture which encourages it?" Scientific discoveries and technology cannot be shelved because of real or imaginary dangers, and it may certainly be predicted that the evolution of physical control of the brain and the acquisition of knowledge derived from it will continue at an accelerated pace, pointing hopefully toward the development of a more intelligent and peaceful mind of the species without loss of

individual identity, and toward the exploitation of the most suitable kind of feedback mechanism: the human brain studying the human brain.

ACKNOWLEDGMENTS

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THREE VIEWS OF THE NERVOUS SYSTEM

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JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN

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Frederick Tilney, *The Brain in Relation to Behavior;* March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values;* April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man;* April 24, 1934

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John F. Fulton, *A Functional Approach to the Evolution of the Primate Brain;* May 2, 1940

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S. R. Detwiler, *Structure-Function Correlations in the Developing Nervous System as Studied by Experimental Methods;* May 8, 1947

Tilly Edinger, *The Evolution of the Brain;* May 20, 1948

Donald O. Hebb, *Evolution of Thought and Emotion;* April 20, 1949

Ward Campbell Halstead, *Brain and Intelligence;* April 26, 1950

Harry F. Harlow, *The Brain and Learned Behavior;* May 10, 1951

Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex;* May 7, 1952

Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History;* May 21, 1953

THREE VIEWS OF THE
NERVOUS SYSTEM

INTRODUCTION

The theme of the James Arthur Lecture series is the evolution of the human brain. Taken in its broadest functional sense, this topic is the most baffling that faces biology today, for man is trying to understand the instrument of his own intelligence. Part of the problem is that there is at present no hint of a "break-through"—nothing equivalent to the elucidation of the DNA structure that led to such an upsurge of work on the mechanisms of inheritance. The only recourse is attacks on the problem from many directions, some seemingly oblique and indirect. One of these directions seeks to understand how simpler nervous systems determine adaptive behavior.

This may be taken as a formal justification for my presence here, although the truth is that I work with insect nervous systems because I enjoy it. But one cannot remain absorbed in any specialty for thirty years without wondering about its wider implications. Therefore, I welcome this chance to discuss the working of the nervous systems of insects in relation to the way insects behave, and to search for a view of my interest set in a wider framework.

INSECTS AND VERTEBRATES

Insects and vertebrates compete ecologically to a degree found in no other two classes of land animals. Man, as the dominant vertebrate, bears the brunt of this competition. There are mutterings in some quarters about the advantage to man in the extermination of this or that insect species

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or even of whole insect groups. To my mind it makes better biological sense to compare the workings of our competitors with our own with the object of outmaneuvering them rather than exterminating them.

Insects and vertebrates represent widely divergent branches of the phylogenetic tree. Consequently, they show striking contrasts as well as similarities. Because these contrasts and similarities are important to my general theme, I shall begin by commenting briefly on examples of each.

Some of the contrasts are self-evident. Approximately one million insect species have been described, and it is estimated that millions more await description. Approximately thirty thousand vertebrate species have been catalogued. Individuals of the great majority of insect species weigh less than one-tenth of an ounce; some vertebrates weigh many tons. This is not the place to discuss the architectural plan of the insect skeleton and how it has imposed a mechanical upper limit on its body size. An important corollary of this size limitation, however, is that insect nervous systems are correspondingly small, even though some of their neurons are as large as or larger than our own. It follows that insect nervous systems must contain fewer neurons, and that there must be parsimony in the way neurons are involved in the multifarious patterns of insect behavior. I shall try to illustrate this at a later point.

Insect and vertebrate similarities are, at first glance, less apparent. It is generally true, however, that if one dissects different animals and inspects their body mechanisms, the similarities become more apparent as the grain of the inspection becomes finer. For instance, at the molecular level nearly all living things find a common ground. At a coarser level, say, that of the light microscope, it is still much easier to determine by inspection what the tissues are for, that is, contraction, conduction, or secretion, than it is to

say whether they belong to an insect or to a vertebrate. This is also true when such tissues are functionally examined. For instance, insect neurons and vertebrate neurons seem to operate on the same general principles.

THREE VIEWPOINTS

Comparing the workings of insect and human brains is like trying to understand a strange and primitive culture from the viewpoint of our own civilization. The outward cultural expressions—mores, economics, religion, and "foreign policy"—seem to us quite difficult to understand, and we can make only blanket generalizations from an external study. On learning more about individual members of that culture, we find that they are very like ourselves and that they have the same joys, anxieties, and motivations. The last and most difficult stage of understanding is to learn how individual members of the citizenry relate to their fellows to form the cultural mesh that determines the image of the strange land.

I shall try to present what I know about insect brains and behavior from three similar viewpoints. First I shall discuss in a general fashion the functions of the insect brain in relation to certain behavioral patterns. Next, I shall summarize the main attributes of that common denominator of all higher nervous systems, the neuron. Finally, I shall attempt the most difficult task of all—to examine how neurons transpose signals from the outer world and interact with other neurons forming the neural mesh to generate an adaptive behavioral pattern.

THE INSECT BRAIN

For an overview of any nervous system, it is best to begin by glancing at its origins. Insect ancestors were probably wormlike forms having a series of similar body

segments (fig. 1A). The activities of each body segment were largely autonomous and were controlled by a ganglion or, rather, a bilateral ganglion pair. The ganglia were serially connected by a pair of longitudinal bundles of nerve fibers. These connectives played little part in determining the local affairs of the individual segments and
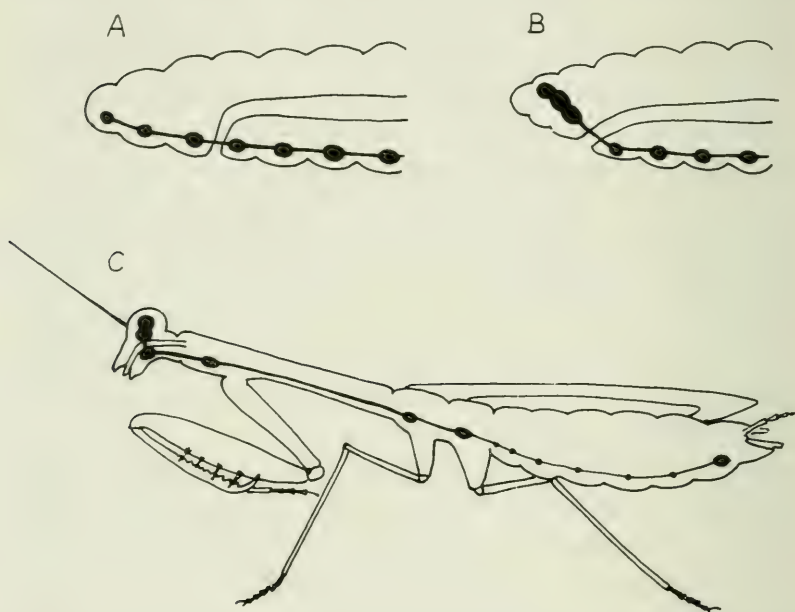

FIG. 1. A. Nervous system of hypothetical ancestor of segmented worms. B. Later stage in the evolution of the arthropod brain. The three anterior ganglia have moved to a dorsal position and have become practically fused. C. Nervous system of the praying mantis. A relatively unspecialized insect nervous system with most of the ventral ganglia distinctly separated. The front pair of legs are specialized for grasping prey.

served mainly to coordinate rapid movements such as those needed in evading a predator. The system of the worm can be likened to a group of self-sufficient rural communities that resort to cooperation only when faced by a general threat.

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At least three, and possibly more, of these ganglia lay in front of the ventrally placed mouth of the worm. The remainder were arrayed behind it and along the ventral surface of the segment chain. The mouth moved to the front end of this primitive creature (the logical spot for gathering food), and the anterior ganglia came to assume a dorsal position while fusing to form a brain (fig. 1B). As the worm became more mobile its "distance" receptors, vision and chemo-reception, clustered at its front end and became more complex and discriminating. Neurons subserving them multiplied, forming the bulk of the adjacent brain.

Broadly speaking, the nervous systems of insects still follow this plan (fig. 1C). The organs of vision and olfaction have increased enormously in complexity and diversity, and corresponding regions of the brain have enlarged accordingly. Similarly, many of the body segments and their appendages have diversified for walking, grasping, hopping, swimming, flying, egg laying, and copulating. Others have atrophied or become fused with their neighbors. The segmental ganglia, however, still retain much of their primitive autonomy in coordinating and regulating the local muscle sequences needed for these special action patterns. The brain plays no part in determining which, or in what order, the muscles of a given segment will contract in performing a given action. This is determined by the relevant segmental ganglion or by the ganglia of a few adjacent segments acting in concert, as in the coordination of the three pairs of legs during walking.

CONTROL BY INHIBITION

At first glance, this arrangement seems to leave the brain with no higher function beyond that needed to process the information coming from the eyes and antennae. There is much evidence, however, that the brain exerts what might

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be called an over-all direction, or command function, in determining the particular action pattern or behavior mode shown by the whole insect under a particular set of conditions. This control seems to be exerted primarily through selective suppression of certain of the locally organized action patterns, the behavioral mode shown at any given moment being released from this suppression. This conclusion is based on experiments such as the following.

The praying mantis waits in ambush for its food, and thus remains motionless most of the time; after removal of its brain a mantis walks continuously (Roeder, 1937). Most insects exhibit sexual behavior only in the presence of appropriate releasing stimuli provided by the opposite sex; decapitated male mantids make continuous copulatory movements irrespective of the presence of a female (Roeder, 1935). Ovipository behavior seems to be similarly controlled. The motor patterns responsible for song production in crickets are coordinated by the thoracic ganglia, yet song patterns specifically connected with different courtship phases can be released in inappropriate circumstances by electrical stimulation of certain regions of the brain (Huber, 1960, 1967). Flapping of the wings in flight normally ceases as soon as the feet of an insect touch the ground. If the insect is, however, decapitated while in flight this natural "either 'or" method of replacing the flight mode by the walking mode is often ineffective, the insect continuing in its attempt to fly even after tarsal contact has been made.

These examples suggest that a considerable proportion of the direction from the head ganglia is accomplished by proscription, that is, by selective suppression of specific activities generated and organized in the ganglia of the several body segments. There is further evidence that inhibition may occur at several levels within the brain. Centers

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in the right and left halves having inhibitory control over activities organized at a lower level may also inhibit one another (Roeder, 1937). Although the brain seems to have this "either or" control over what the whole insect does, the same principle extends to the local segmental activities presided over by the segmental ganglia. This is evident in the control of alternate stepping movements of the right and left legs of a segment and in the control of grooming behavior in locusts (Rowell, 1965).

THE "ONENESS" OF BEHAVIOR

One of the most commonplace, but to me most remarkable, aspects of the behavior of animals is the "oneness" or singularity of their acts. An animal seems able to select just one mode of behavior even under such circumstances as being exposed to stimuli capable at other times of releasing a wide variety of behavior patterns. It is easy to justify the adaptive value of this unity of response, but, regarded mechanistically, it seems surprising that a system with so many input channels should so rarely compromise between conflicting signals. In essence, this problem is one of "attention," which is no less marked in insects than in higher animals. It is also present at lower levels of the nervous system, for the reflex contraction of one muscle group automatically inhibits the contraction of its antagonist muscles.

Do the command functions of the insect brain play a part in this "oneness" of behavior? In releasing one behavioral pattern does the brain increase the suppression of others? If such is the case one would expect to observe conflicting behavior patterns in a brainless insect.

There is some evidence for this. A praying mantis normally remains motionless for hours at a time, waiting in ambush at the top of a vertical surface. From this vantage

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point it strikes at passing insects which are grasped in its specially modified forelegs. If placed on the ground a mantis will usually walk until it encounters a vertical object, such as a plant stem. It then climbs to the top of this object and remains motionless in the in-ambush posture. After the removal of its brain, however, a mantis walks continually, persisting in its attempts to travel forward even after reaching the top of a vertical object. If, during these travels, a twig or other small object happens to touch the inner, spined surface of its foreleg, the object is grasped firmly and persistently. The insect appears to be unable to release its grip even though this action may impede further forward progress. The action of grasping does not, however, suppress continuous attempts to walk forward, with the result that the insect frequently becomes hopelessly entangled in twigs and grass stems (Roeder, 1937). It might be thought that this abnormal behavior is due to sensory deprivation, but it is not produced by removal of the eyes, optic ganglia, or antennae. In the intact insect the two action patterns (grasping and walking) rarely, if ever, occur simultaneously, and their simultaneous appearance in the brainless mantis places the insect in a behavioral cul-de-sac. This suggests that, when the brain is present, either one, or neither, but never both, of these behavioral modes is released.

ENDOGENOUS ACTIVITY

There is little detailed physiological information as to how these segmentally determined activities are organized. Nor do we understand the nature of the inhibition that patterns them locally and controls them selectively from the brain. In some cases inhibition appears to operate by raising the threshold of a locally organized reflex response, that is, by rendering it less likely to occur. This is seen in

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the grasping reflex of the mantis described above and in the grooming reflexes of locusts (Rowell, 1965). In other cases the segmental neural systems seem to be intrinsically unstable, that is, capable of endogenous generation of behavior patterns. Organized sequences of nerve impulses are transmitted to appropriate muscles even after the ganglion has been deprived of all sensory input. This has been shown to be the case with copulatory movements generated by the last abdominal ganglion of the male praying mantis (Roeder, Tozian, and Weiant, 1960) and with wing flapping in locusts (Wilson, 1961, 1967).

It has long been known (Adrian, 1931) that insect ganglia discharge patterns of impulses for considerable periods after they have been isolated from all sensory input. Some of this endogenous activity may be abnormal (Rowell, 1965), that is, caused by the surgical insult and unrelated to normal behavior. In the two cases cited above, however, endogenous neural activity seems to be the basis for movements that have significance in the lives of the animals concerned. There is, indeed, no satisfactory way to distinguish between a reflex response, the threshold of which has been reduced to extremely low levels, and a system that is endogenous or self-excitatory (Roeder, 1955).

THE BEHAVIOR OF NEURONS

So far, I have considered only the external or behavioral signs of nervous system function. I have glanced, as it were, at the "foreign policy" of the cell community that makes up an animal. In the preceding paragraph it was necessary to mention neurons and nerve impulses. Neurons are the unit components of the nervous system or, if you prefer the sociological analogy, members of the community that formulate the foreign policy. Somehow, the details of the mass transactions between brain and ventral ganglia must

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originate in transactions between neurons. Such transactions are accomplished mainly through nerve impulses.

It is perhaps as misleading to generalize about a "neuron" as it is to generalize about a "person." The transactions of neurons in the central nervous system have been most closely scrutinized in studies of vertebrates, particularly through the monumental work of Eccles (1953, 1964) on the spinal cord of the cat. There is no evidence that insect neurons operate on basically different principles, so I shall draw largely on this work in making my brief generalizations.

The central nervous system can be regarded as an organized mesh of nerve fibers. Extending into this mesh are fibers from a multitude of sensory neurons (sense cells) that are acted upon by the outer world. Out of the mesh extend fibers belonging to motor neurons. These connect with effectors—the muscle fibers and gland cells that act upon the outer world. The patterning of muscle contractions that manifests itself as behavior is determined in part by the organization and functional state of neurons forming the central mesh and in part by the pattern of input signals reaching the central mesh from sensory neurons.

Those neurons lying entirely within the central mesh are called interneurons. They are of many sizes and configurations and have many ways of interacting. I must neglect entirely the interactions based on neurosecretion and hormones, and will limit this discussion to rapid, short-term, neuron transactions carried out by means of nerve impulses.

A generalized diagram of an insect interneuron is shown in figure 2. It receives excitation from impulses arriving at close contacts (synapses) after traveling in nerve fibers (axons) belonging to other neurons. Nerve impulses can be detected as small, transient, electrical

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"spikes" propagating along a nerve fiber. Information is contained in the frequency, timing, and pattern with which nerve impulses recur.
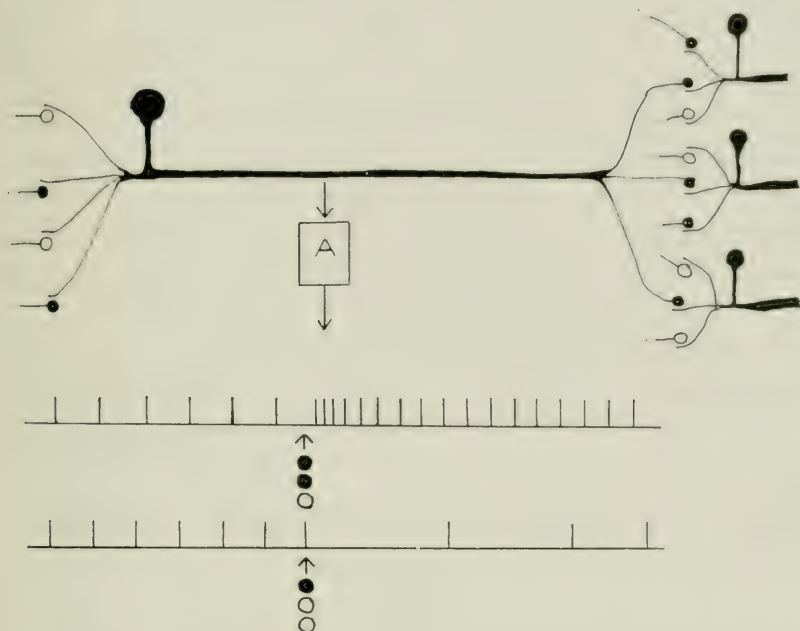

FIG. 2. A generalized diagram of an insect interneuron. At left, four pre-synaptic fibers make two inhibitory (open circles) and two excitatory (solid circles) contacts with its dendrites. The axon of the interneuron forms excitatory synapses with other interneurons (at left). An electrode (arrow) leading to an amplifier (A) registers the pattern of spikes discharged by the interneuron. When presynaptic impulses arrive at two excitatory and one inhibitory synapse (upper trace), the integrated result is an increase above the free-running spike frequency. Activity of two inhibitory and one excitatory synapse (lower trace) causes a decrease in spike frequency.

Synaptic contacts are of several kinds and are often highly complex, but in the present context their most important property is that most of them represent a hiatus or hindrance to the process of impulse propagation through the mesh. This means that the arrival of an impulse at an

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excitatory synapse does not generate in one-to-one fashion another impulse in the downstream neuron. It merely increases for a few milliseconds the *tendency* of the recipient neuron to fire off an impulse of its own. The excitatory state wanes exponentially. This means that impulses arriving roughly coincidentally at neighboring synapses formed on the same interneuron will summate in promoting the firing tendency of the neuron, which may cause it either to discharge impulses or, if it is already active, to increase its firing rate (fig. 2). In the same way, impulses arriving with greater frequency at a given synapse summate in their effects on the recipient neuron to a greater degree than if they impinge on it at more extended intervals.

A proportion of the synapses formed on many interneurons are inhibitory. The arrival of an impulse at an inhibitory synapse decreases for a few milliseconds the tendency of the recipient neuron to fire off an impulse of its own. The collective effects of impulses arriving at several inhibitory synapses summate in time and space as do those arriving at excitatory synapses, and the effects of both types are continuously integrated by the recipient interneuron. Thus, one must picture an interneuron as being exposed to a running barrage of excitatory and inhibitory effects, each with a "half-life" of a few milliseconds. Its own discharge pattern reflect the running integration of this barrage. Elsewhere (Roeder, 1967b) I have compared the activity of an interneuron to the actions taken by an administrator. He bases his actions on decisions reached by integrating the positive and negative opinions of others, the most recent opinions being the most influential. Some interneurons, like lower-level administrators, merely relay forward the impulse pattern reaching their synapses. But in the central nervous system these are probably in the minority, and in any case their behavior is relatively unin-

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teresting in our efforts to understand the transactions of the brain.

References must be made to other sources (Eccles, 1953, 1964) for the details of synaptic action, chemical effects, types of synapse, and the complex feedback arrangements found in neuron populations. The point is that synaptic interaction of neurons is the only known way in which fast-acting integrations and transformations of the central nervous system are carried out. Admittedly, it is hard to believe that higher nervous functions, such as learning, memory, and abstract thought, are based only on such a system. New modes of neuron interaction and special properties that emerge from the mesh may be discovered, but it must be realized that it would be hard to predict the properties of a computer if one were given only the properties of a single transistor.

Next, I shall attempt to describe some of the neuron signals and transactions concerned in a relatively simple piece of insect behavior.

MOTHS AND BATS

It is observed that a certain pattern of stimuli impinging on an animal bears a causal relation to action having adaptive value. The problem facing the neurophysiologist is to untangle the mechanisms transforming stimulus into action. Commonly, the problem is formidable at the outset; the stimulus pattern may be complex and hence difficult to define in physical or chemical terms, and it usually impinges on the animal via thousands of receptor neurons, each having a separate fiber leading to the central nervous system. Therefore, many pathways must be monitored simultaneously in order to assess fully the incoming sensory information. The initial difficulty is often insurmountable, but it must be overcome before one can know, in terms
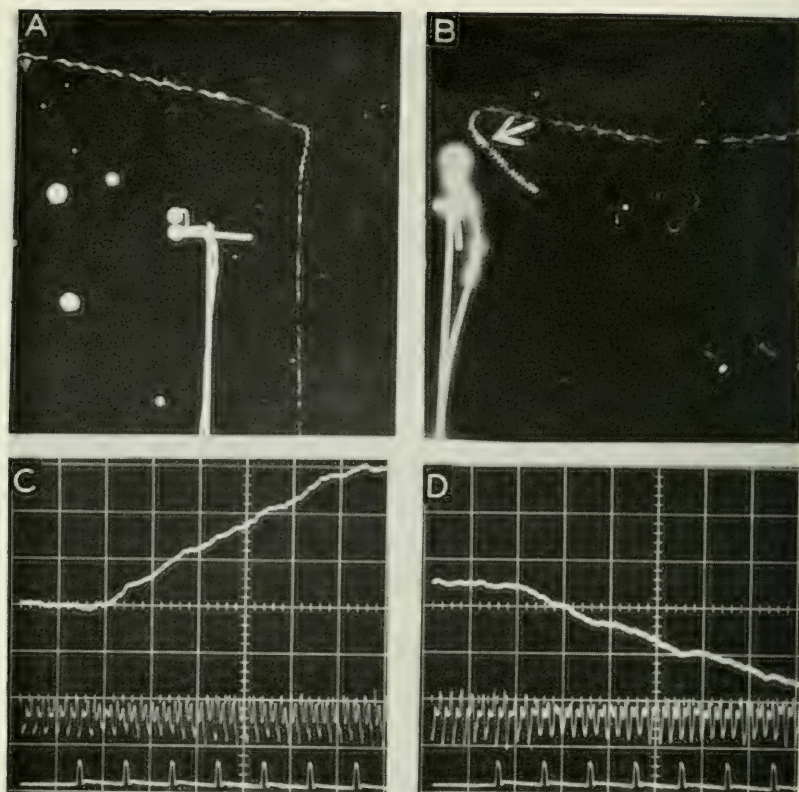
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FIG. 3. A, B. Photographic tracks registered by moths flying free in the field at night. The loudspeaker on the mast began emitting a series of ultrasonic pulses in simulation of a bat at the instant indicated by the bright spot in A and by the arrow in B. The tracks have breaks every 0.25 second. The oscillations on the tracks are due to the flapping wings of the moths. A. Diving in response to a loud sound. B. Turning-away in response to a faint sound (Roeder, 1962). B, C. Electronic registration of the attempts of a captive moth to turn away from a loudspeaker emitting a train of faint ultrasonic pulses. Upward deflection (top trace) indicates an attempt to make a right turn; downward deflection, an attempt to turn left. Middle trace shows wing movemens of moth. Lower trace indicates onset of pulse train (10 per second). Vertical grid marks 100-milli-second intervals. C. Loudspeaker was in horizontal plane and at 90 degrees to body axis of moth on left side. D. Same, loudspeaker on right side. Attempts to turn away began about 50 milliseconds after first sound pulse. The moth was a female of *Leucania commoides* (Roeder, 1967).

of nerve impulse patterns, how the outer world is being reported to the central nervous system under the given

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circumstances. The example I wish to present overcomes this initial difficulty.

Several species of insectivorous bats of North America fly and feed in darkness. They use a kind of sonar to avoid obstacles in their path and to find, track, and capture flying insects. The operation of this sonar has been clarified by the elegant work of Griffin and his students (1958). A cruising bat emits a series of ultrasonic cries and appears to be able to estimate the distance and direction of objects in its flight path from changes in the echoes returning to
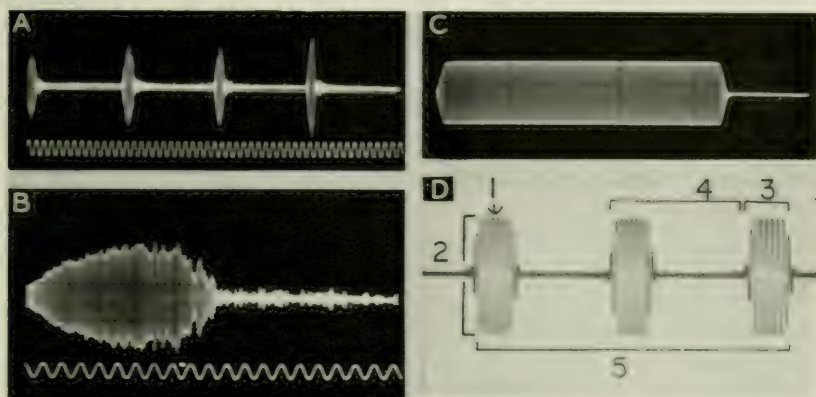
Fig. 4. A. Ultrasonic cries recorded from a cruising bat flying in the field. Time, 100 cycles per second. B. A Single cry on expanded time base. Time, 1000 cycles per second. C. Artificial ultrasonic pulse similar to those used in the experiments described in the text. Vertical grid, 2-milliseconds per division. D. Diagram showing the individually variable parameters of the stimulus: 1, frequency; 2, amplitude; 3, pulse duration; 4, pulse repetition rate; 5, pulse train length.

its ears. The range of this sonar system for an object the size of a flying moth appears to be less than 10 feet.

Moths of several families, notably the Noctuidae, have auditory organs maximally sensitive to the pitch of bat cries. They serve the moth as counter-sonar detectors, and they are able to register bat cries at distances of up to 130

feet (Roeder, 1966a). Moths show two types of reaction when they are exposed to real or simulated bat cries (fig. 3A, B). If the sounds reach the moths at high intensity, as from a nearby bat, the insects show various kinds of unpredictable behavior, such as twisting, turning, and diving toward the ground. If the sounds are received at low intensity, for example, by a moth flying 50 to 100 feet distant from a hunting bat, the moth turns and steers a course directly away from the source of the ultrasonic pulses (Roeder, 1962).

The survival value of turning-away behavior is fairly clear. It carries the slower-flying moth out of the feeding area of the bat before its presence has been detected by the sonar of the predator. Turning-away behavior has been examined more closely (Roeder, 1967a; also fig. 3C, D). When a moth is mounted in stationary flight (attached to a support) and exposed to faint ultrasonic pulses from a loudspeaker placed either to its right or its left, the moth begins its attempt to turn away 45 milliseconds after the beginning of stimulation. The experiments (fig. 3C, D) show that it is able to choose the correct direction (right or left) after receiving only the first pulse of the series, and that it makes the change in flight direction by partially folding its wings on the side of the body away from the sound source.

THE ACOUSTIC SIGNAL AND THE EAR OF THE MOTH

These facts narrow the search for what takes place between the arrival of a stimulus and the change in flight direction. Two other circumstances give additional encouragement to the search.

First, the cries made by a bat (fig. 4A, B) can be duplicated electronically (fig. 4C) with sufficient accuracy to produce turning-away behavior. The artificial signal may

be said to have five different parameters or dimensions, each of which can be varied independently. It is possible, therefore, to determine what aspects of the cries of a bat will release and steer the evasive behavior of a moth. The five parameters of the stimulus (fig. 4D) are: (1) the frequency (pitch) of each sound pulse; (2) the amplitude (intensity) of each pulse; (3) the duration of each pulse; (4) the interval between pulses (repetition rate); and (5) the duration of the whole pulse train.

The present question is: How are these parameters translated or encoded by nerve-impulse patterns coming from the ear of the moth and integrated by interneurons in its central nervous system? The question may be put slightly differently: Which of these parameters is significant in determining what the moth finally does?

The second encouraging circumstance is the extreme anatomical simplicity of the ear of a moth, which was pointed out more than forty years ago (Eggers, 1925). A noctuid moth has only two receptor cells in each ear, compared with about fifty thousand in each ear of a human being. Such a difference is a striking example of the parsimonious distribution of neurons in insect nervous systems mentioned above. Practically, it simplifies the task of reading out and assessing the total information reaching the central nervous system of the moth via the channel that connects it with the outside world. Electrodes can be placed on the acoustic nerve, and the spike patterns delivered by these two sense cells are readily interpreted under different conditions of stimulation.

The details of the ear of a moth are shown in figure 5. The bipolar sense cells (A_1 and A_2) are connected to the eardrum by fine and complex organelles that transduce the acoustic energy into a train of nerve impulses. The central ends of A_1 and A_2 extend as two nerve fibers in the tym-
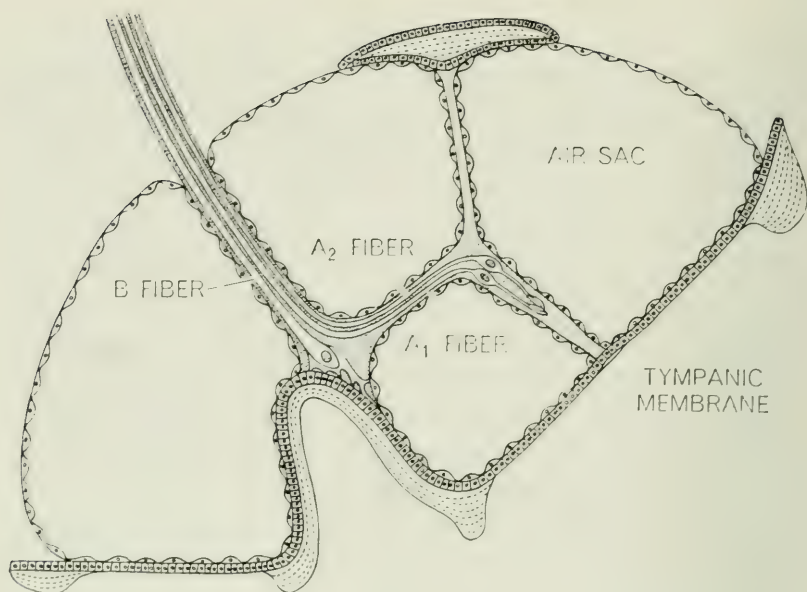
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Fig. 5. Diagram of dorsal view of the right tympanic organ of a noctuid moth. The tympanic membrane faces obliquely rearward and outward into the constriction between thorax and abdomen. The scoloparium is a thin strand of tissue attached to the inner surface of the tympanic membrane and suspended in the air-filled sac by a ligament (top). The acoustic sense cells, A_1 and A_2, lie in the scoloparium. Their distal processes, extending toward the tympanic membrane, transform sound energy into a series of nerve impulses, transmitted to the central nervous system by the A_1 and A_2 nerve fibers. The B fiber arises from a non-acoustic sense cell, serving probably to register mechanical distortions of the tympanic organ. Courtesy of *Scientific American*.

panic nerve connecting with the pterothoracic ganglion. This nerve mass, which consists of the second and third thoracic ganglia, is the site for the major neuronal transactions concerned in bat avoidance.

NEURAL TRANSFORMATIONS AND TRANSACTIONS

The traffic of nerve impulses flowing from the tympanic organ to the central nervous system is detected by an electrode placed on the tympanic nerve. The sequence of frames (fig. 6) shows how the spike patterns generated by the more sensitive sense cell (A_1) changes as the intensity

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of a brief, ultrasonic pulse is increased by measured steps.
As the sound becomes louder, the spike pattern changes in
several respects: (a) more spikes are generated, that is,
a longer train is produced, although the duration of the
stimulus remains constant; (b) the spikes are more closely
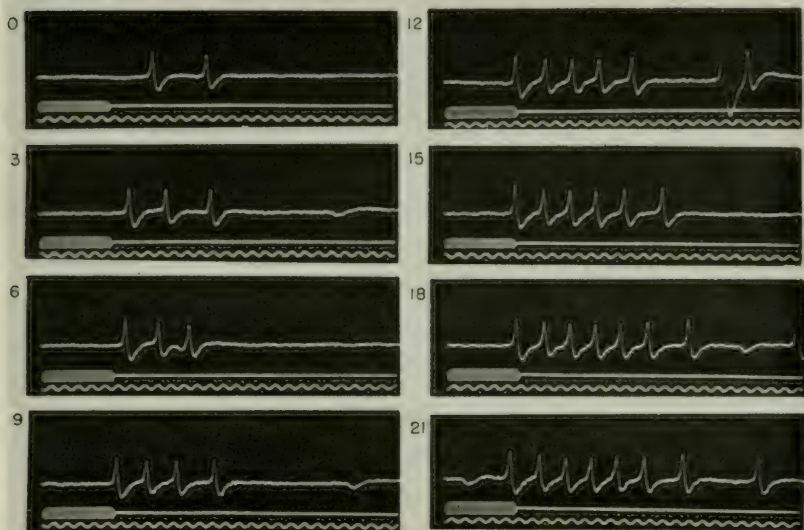spaced; (c) the latency or interval between the stimulus

FIG. 6. Spike responses (upper traces) recorded from an electrode on the
tympanic nerve of the moth, *Xylena curvimacula*, when pulses of 25 kilohertz
and 5 milliseconds in duration (middle traces) were directed at the ear. Sound
intensities are given in decibels above an arbitrary value (0) producing a minimal
acoustic response. Time marker (lower traces), 1000 cycles per second.

and the first spike of the series becomes less; and (d) at
lower intensities only the sense cell A_1 is stimulated, where-
as, at sound intensities ten times greater, it is joined by
responses of the A_2 sense cell (not shown in fig. 6).

Stated in another way, a hypothetical homunculus, sta-
tioned at the central termination of one tympanic nerve
in the thoracic ganglion, could determine intensity differ-

ences in the stimulus by four different criteria, not all of them equally good. Criterion "a" might be ambiguous in pulse duration, a longer pulse being confused with a louder pulse. Criterion "b" would give a fairly accurate measure of differences in pulse loudness. Criterion "c" would be useful to the homunculus only if he could compare signals coming from the right and left ears in response to the same sound pulse. Criterion "d" would be a rough measure and useful only in comparing very large differences in sound intensity. Because we are concerned solely with the neuronal mechanism of turning-away, which occurs at intensities capable of exciting only the A_1 sense cells, criterion "d" can be neglected.

The same experiment, carried out with sound pulses of different frequency (parameter 1), gives the same results over a wide frequency range, roughly 15 to 100 kilohertz. Thus, the moth appears to be tone deaf. The homunculus could not measure parameter 1 from the spike signals reaching him, although inspection of figure 6 shows that the other four parameters of the stimulus are measured in the spike pattern generated by the sense cells.

The next step is to find interneurons influenced by the A_1 signal and to determine in what ways they further transform the spike pattern. A metallic microelectrode is lowered into the ganglion and used as an electrical probe. It is moved about in search of the A_1 signal and of events showing some causal relation to it.

From here on the trail becomes confused by a babel of spike patterns, mostly of unknown origin and significance. The A_1 pattern is easily recognized (fig. 7A). It reaches the ganglion 3 to 5 milliseconds after sound reaches the tympanic organ. Downstream from this point in the neuronal mesh a number of interneurons have been encountered whose signals show various types of relation to the

A₁ response (Roeder, 1966b). I shall mention only three of these, as they hint at ways in which the central nervous system may convert stimulation into behavior.

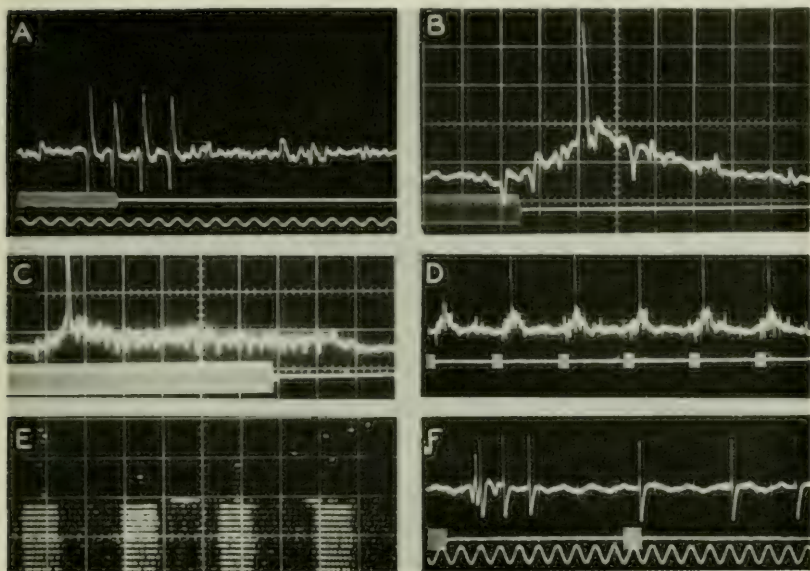The pulse-marker neuron is excited by a train of three

Fig. 7. Responses to stimulation of the tympanic organ recorded with microelectrode from sensory and interneurons in the pterothoracic ganglion of noctuid moths (*Caenurgina erechtea* and *Heliothis zea*). A. A₁ spikes recorded from neuropile in response to a 5-millisecond ultrasonic pulse (middle trace); time (lower trace), 1000 cycles per second. B. A₁ spikes (small downward deflections) and single pulse-marker spike (large upward deflection) in response to 5-millisecond sound pulse (lower trace). Time, 2 milliseconds per division. C. The same, response to a longer (38-millisecond) sound pulse. Time, 5 milliseconds per division. D. Single pulse-marker spike recurring in response to each of a series of short ultrasonic pulses (lower trace) repeated 40 times a second. E. Train-marker response. Spikes are indicated as dots on a raster that should be read like consecutive lines on a printed page. Groups of larger dots are A₁ spikes, and indicate parameters 2-5 of the stimulus. Smaller dots are train-marker spikes, recurring at a frequency independent of the pulse repetition rate throughout the stimulation period. F. Change in the pattern of spikes in the motor nerve supplying a muscle controlling extension of the forewing in response to stimulation of the tympanic organ (middle trace). Motor response begins about 20 milliseconds after first sound pulse reaches the ear. Second sound pulse appears to have no effect. Time, 100 cycles per second.

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or four A_1 impulses coming from the ear on the same side of the body (fig. 7B). The synaptic effects of the A_1 impulses produce sufficient summation to trigger the pulse-marker only if they are separated by intervals of 2 milliseconds or less. Typically, the response of the pulse-marker is a single large spike, irrespective of the duration of the stimulating sound pulse (parameter 3) and of the resulting train of A spikes that impinges upon it. This curious behavior of the pulse-marker (one spike per ultrasonic pulse irrespective of its duration) seems to depend on a neuronal mechanism that requires 4 or 5 milliseconds without synaptic bombardment by A_1 impulses in order that the interneuron be "reset" to respond. This pause does not occur when a long and moderately intense pulse reaches the ear (fig. 7C). The pulse-marker will, however, generate spikes up to 40 times per second if the long pulse is broken into short pulses (fig. 7D). This behavior is interesting in three respects.

First, the pulse-marker spike transmitted downstream can be said to have discarded parameters 2 and 3 as defined by the original ultrasonic stimulus. A homunculus observing only the signal generated by one pulse-marker could not judge differences either in the intensity or in the duration of the original stimulus. He could still determine pulse intervals (parameter 4) and the duration of the pulse train (parameter 5).

Second, pulse-markers connected to the right and left ears and sending their spikes into a mechanism that compared relative times of arrival would be capable of steering a moth in flight away from a distant sound source, because the latency of the pulse-marker spike is long and variable, depending as it does on the arrival of three or four A spikes at sufficiently short intervals. Therefore the latency is inversely related to intensity, and relative intensity (right versus left ear) could be determined by marking whether

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the right or the left pulse-marker fired first in response to a given pulse. A neuronal mechanism making such a comparison has not yet been found.

Third, the behavior of the pulse-marker shows a striking correlation with the behavior of flying moths exposed to different ultrasonic pulse patterns (Roeder, 1964, 1967a). Long, continuous tones produce only transitory turning-away or none at all, whereas pulsed ultrasound causes a sustained attempt to turn.

Among the neurons the signals of which have been intercepted, two others seem relevant to the present account. The first has been termed the train-marker neuron.

The train-marker neuron is inactive during silence, but begins to discharge a train of spikes at an independent frequency throughout the period in which a train of ultrasonic pulses reaches the ear (fig. 7E). The spike repetition rate of the train-marker bears no relation to the pulse repetition rate of the stimulus. Thus, the homunculus provided only with the train-marker signal would be able to measure only the duration of a pulse train (parameter 5). The other parameters of the stimulus would be lost to him.

Another interneuron, rarely encountered, appears to add the A_1 signals coming from the right and left ears. It fires twice as many spikes when both ears are stimulated as when either ear alone is exposed to ultrasonic pulses.

TURNING-AWAY

These and other bits of information (Roeder, 1966b, 1967b) are insufficient for a definition of the neuronal mechanism that is responsible for turning-away behavior. The reason may be likened to the uncertainty principle in physics—the deeper one searches for answers the greater is the disturbance created by one's searching methods in the beautifully poised living system. But one is heartened by

the hope that the biological obstacles are mainly technical rather than theoretical as in the uncertainty principle facing the physicists.

Many attempts have been made to approach the turning-away response from the motor end, but the percentage of success has been very small. In a few cases changes in the pattern of motor impulses traveling to the wing-folding muscles have been registered when the ear had been stimulated with ultrasonic pulses (fig. 7E).

Incomplete though they are, the data presented give

TABLE 1

PARAMETERS OF THE ULTRASONIC STIMULUS PRESENT
IN VARIOUS SIGNAL PATTERNS

Signal Pattern of	1 Frequency	2 Amplitude	3 Duration	4 Pulse Interval	5 Train Length
Stimulus	X	X	X	X	X
Tympanic nerve	—	X	X	X	X
Pulse-marker	—	—	—	X	X
Train-marker	—	—	—	—	X
Turning-away behavior	—	—	—	a	X

a Not present at the pulse repetition rates in bat cries.

hints as to the *kind* of processing occurring in the central nervous system. The original stimulus had five variable parameters. The first of these, frequency (parameter 1), is omitted from the tympanic nerve signal. Similar stages in which other parameters are discarded are represented by the pulse-marker (parameters 2 and 3) and the train-marker (parameter 4) interneurons (table 1). It is as if each parameter present in the original stimulus is a separate key that permits admittance to a specific door but becomes useless once the door in question has been passed.

At this point it seems worthwhile to compare the informational content regarding the original stimulus that

is contained in the signal patterns registered at various points in the nervous system of the moth with that contained in its ultimate reaction—the turning-away behavior. Such a comparison is summarized in table 1. A train of sound pulses reaching one ear at higher intensity causes a steady, sustained attempt to turn away from the stimulus. A continuous tone or a single pulse causes only a transitory turning attempt. As the table shows, an observer of this behavior could infer from it only the direction and the pulse-train length of the stimulus; none of the other param-- eters of the original stimulus would be reflected in the response. The neurophysiological experiments summarized in table 1 suggest some of the steps in this elimination of stimulus parameters as nerve signals propagate through the nervous system and eventually shape the reaction of a moth to a passing bat.

CONCLUSION

The mechanisms whereby nervous systems generate adaptive behavior have been regarded from three different viewpoints. The first, which might be called the "center" viewpoint, observes changes in behavior following relatively massive surgical interference with the sense organs or with parts of the central nervous system. It provides only a broad picture of the functional topology of the nervous system, and leads to concepts of "regions," or "centers," interacting with each other. The center viewpoint has been of particular heuristic value in anlayzing insect nervous systems because insect ganglia show a high degree of anatomic separation, which is to some extent correlated with function. For instance, it suggests that the insect brain determines the "oneness," or "singularity," that is so universal in animal behavior. Such determination is accomplished under given conditions by the inhibition of all but

one of the action patterns organized by the segmental ganglia.

At the present time, the center viewpoint seems unrelated to the much closer and more fine-grained viewpoint of modern neurophysiology. Indeed, its conclusions do not even require the postulation of neurons, nerve impulses, or synapses. When regarded from the viewpoint of neurophysiology, the widely separated phylogenies of insect and vertebrate nervous systems find a common base in the behavior of single neurons. But when observed only from the tip of a mircoelectrode differences between these two groups of animals become mainly quantitative. There, the second, or neuron, viewpoint also has its limitations.

The third viewpoint takes the findings of neurophysiology for its basic assumptions. Given the intramural properties of neurons, it is concerned with neuron interaction, with information transfer in neuron populations, and with the way these and other functions could transpose a stimulus pattern significant in the life of an animal into a response promoting its survival.

At present, the neuron communities that can be comprehended from this viewpoint are small and simple, several orders of magnitude simpler than those that are the concern of the center viewpoint. Attempts to describe behavior in terms of neuron populations are in their infancy. An infant can handle, however, only simple toys, and hence I believe that the simpler neuron communities—the nervous systems of insects—have much to offer.

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THIRTY-NINTH
JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1970

WHAT MAKES
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JAMES ARTHUR LECTURES ON
THE EVOLUTION OF THE HUMAN BRAIN

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Dominick P. Purpura, *Ontogenesis of Neuronal Organizations in the Mammalian Brain;* May 25, 1967

*Kenneth D. Roeder, *Three Views of the Nervous System;* April 2, 1968

†Phillip V. Tobias, *Some Aspects of the Fossil Evidence on the Evolution of the Hominid Brain;* April 2, 1969

*Karl H. Pribram, *What Makes Man Human;* April 23, 1970

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The hippopotamus may well regard man, with his physical weakness, emotional unpredictability, and mental confusion as a freak. . . .

(Heschel, 1965, p. 23)

CONTENTS

WHAT MAKES MAN HUMAN

Introduction

> *"IN THE MIDDLE AGES THINKERS WERE*
> *TRYING TO DISCOVER PROOFS FOR THE*
> *EXISTENCE OF GOD. TODAY WE SEEM TO*
> *LOOK FOR PROOF FOR THE EXISTENCE OF*
> *MAN."*   *(HESCHEL, 1965, p. 26)*

What makes man human is his brain. This brain is obviously different from those of nonhuman primates. It is larger (Jerison, 1961), shows hemispheric dominance and specialization (Mountcastle, 1962), and is cytoarchitecturally somewhat more generalized (Bailey and von Bonin, 1951; Lashley and Clark, 1945). But are these the essential characteristics that determine the humanness of man? This paper cannot give an answer to this question for the answer is not known. But the problem can be stated more specifically, alternatives spelled out on the basis of available research results, and directions given for further inquiry.

My theme will be that the human brain is so constructed that man, and only man, feels the thrust to make meaningful all his experiences and encounters. Development of this theme demands an analysis of the brain mechanisms that make meaning—and an attempt to define biologically the process of meaning. In this pursuit of meaning a fascinating variety of topics comes into focus: the coding and recoding operations of the brain; how it engenders and processes information and redundancy; and, how it makes possible signs and symbols and propositional utterances. Of these, current research results indicate that only in the making of propositions is man unique—so here perhaps are to be found the keynotes that compose the theme.

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My concern with meaning originated in an attempt to formulate what ails the current educational process (Pribram, 1964, 1969a). Education entails communication between generations. As such, educational institutions have been set up to transmit information. Our schools have rightly been occupied with problems of information storage and retrieval: what ought to be taught in what period of time and how it is to be demonstrably retrieved.

But, it seems this is not enough. From those whom we try to educate we hear rumblings and even shouts of discontent—discontent which arises at least in part from our failure to meet an educational need. What might this be? Is the mere acquisition of information insufficient? May the accumulation of information even be a cause of the problem? Is it not imperative to attempt to impart something additional, something which makes information *meaningful?*

Information measurement theory provides an interesting starting point for inquiry into this question. In an organism endowed with memory the acquisition of information can, on occasion, actually lead to an increase in uncertainty. Take, for instance, a family. The wife is at home, her husband away on a trip, and two children are in college. Her husband informs her that he will call on Thursday, her birthday. Letters from the children give the additional information that they also will call. When the phone rings the wife experiences an amount of uncertainty equivalent to the amount of information she was given initially. She can reduce her uncertainty by obtaining more "information": asking who's calling. But note that though at the moment of the call the answer to her question provides information, when the extended time period over which the entire episode has transpired is considered, the answer

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is a repetition of one of the earlier messages. Thus, over time, uncertainty is countered, not by something novel, not by information, but by redundancy, i.e., by repetition.

My thesis will be that meaning—the gerund of an old English word for intend, give purpose to—is made possible by repetition. Let me spell out this thesis, first in general, then in brain terms. Repetition comes in many forms. Some forms, some patterns of repetition, are more meaningful than others. Patterns of repetition are called codes. Codes are constructed for a useful purpose. When an organism is uncertain he has two alternative strategies to follow: one, he can reduce uncertainty by seeking real novelty, i.e., information. This, as already noted, will often bring only temporary relief because of man's mnemonic capacity. The other strategy is to reduce uncertainty by coding—by enhancing redundancy, repeating the familiar. This carries the penalty of boredom unless the patterns of repetition are varied. Varying a code turns out to be a remarkably powerful instrument for effectively reducing uncertainty because it permits using information in unexpected ways.

From my own research I have concluded that one of the most pervasive—perhaps the most pervasive—of the operations of the brain is, when the need is felt, to actively revise the patterns of redundancy in which information is encoded (Pribram, 1969b). There are several levels of these encoding operations, each useful in its own way. Let me first say something about what a code is and then describe the types of codes constructed by the brain.

What A Code Is

*"WONDER, OR RADICAL AMAZEMENT, IS A
WAY OF GOING BEYOND WHAT IS GIVEN IN
THING AND THOUGHT, REFUSING TO TAKE
ANYTHING FOR GRANTED, TO REGARD ANY-
THING AS FINAL."* (HESCHEL, 1965, pp. 78-79)

Not so long ago my laboratory came into the proud possession of a computer. Very quickly we learned the fun of communicating with this mechanical mentor. Our first encounter involved twelve rather mysterious switches which had to be set up (U) or down (D) in a sequence of patterns, each pattern to be deposited in the computer memory before resetting the switches. Twenty such instructions or patterns constituted what is called the "bootstrap" program. Only after this had been entered could we "talk" to the computer —and it to us—via an attached teletype. For example:

$$D \ U \ U \ U \ U \ U \ D \ D \ D \ D \ U \ D$$
$$D \ D \ D \ D \ D \ D \ D \ D \ U \ U \ D \ D$$
$$D \ U \ U \ U \ D \ D \ U \ D \ U \ U \ U \ D$$
$$D \ U \ D \ D \ U \ D \ D \ D \ U \ U \ D \ U$$
$$D \ D \ U \ D \ D \ D \ D \ U \ U \ U \ U \ U \text{ and so on.}$$

Bootstrapping is not necessarily an occasional occurrence. Whenever a fairly serious mistake is made—and mistakes were made often at the beginning—the computer's control operations are disrupted and we must start anew by bootstrapping.

Imagine setting a dozen switches twenty times and repeating the process from the beginning every time an error is committed. Imagine our annoyance when the bootstrap didn't work because perhaps on the nineteenth instruction an error was made in setting the eighth switch. Obviously, this was no way to proceed.

Computer programmers had early faced this problem and solved it simply. Conceptually, the twelve switches are divided into four triads and each combination of up or down within each triad is given an Arabic numeral. Thus,

```
D  D  D  became  0
D  D  U  became  1
D  U  D  became  2
D  U  U  became  3
U  D  D  became  4
U  D  U  became  5
U  U  D  became  6
U  U  U  became  7
```

Conceptually, switching the first toggle on the right becomes a 1, the next left becomes a 2, the next after this a 4, and the next an 8. If more than a triad of switches had been necessary, if, for instance, our computer had come with sixteen switches, we should have conceptually divided the array into quads. Thus the bootstrapping program now consisted of a sequence of twenty patterns of four Arabic numerals, such as:

```
3  7  2  2
0  0  1  4
3  4  5  6
2  2  1  5
1  0  3  7  etc.
```

and we were surprised at how quickly those who bootstrapped repeatedly, actually came to know the program by heart. Certainly fewer errors were made in depositing the necessary configurations—the entire process was speeded and became, in most cases, rapidly routine and habitual.

Once the computer is bootstrapped it can be talked to via a teletype in simple alphabetical terms, for example, JMP for jump, CLA for clear the accumulator, TAD for

add, etc. But each of these mnemonic devices merely stands for a configuration of switches. In fact, in the computer handbook the arrangement for each mnemonic is given in Arabic notation: e.g. CLA = 7200. This in turn is easily translated into U U U D U D D D D D D D should we be forced to set the switches on the computer by hand because the teletype has gone out of commission.

In the first instance, then, programming is found to be the art of devising codes, codes that when hierarchically organized facilitate learning, remembering and reasoning. The power of the coding process is not to be underestimated. Should you doubt this, try next month to check your bank statement against your record of expenditures and do it all using Roman rather than Arabic numerals. Can you imagine working out our national budget in the Roman system?

Next let me turn to an analysis of the classes of codes engendered by the brain. These must account for the existence of subjective states such as perceptions and feelings; for the achievement of acts in the organism's environment; for the construction of signs and symbols by which organisms communicate with each other; and for the composition of propositions, the tools with which man reasons and has fashioned his culture. Research on the brain mechanisms relevant to each of these classes has in recent years yielded some fascinating surprises (Pribram, 1971). Let me share some of these surprises with you in the search for meaning even if at times the connection between brain, behavior and meaning will appear to be remote. My route is a deliberate one, however, because for me: "Knowing [about meaning has not been] due to coming upon something, naming and explaining it. Knowing has been due to something forcing itself on [me]." (Heschel, 1965, p. 109).

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Brain Function in Awareness

"THE EXPERIENCE OF A MEANING IS AN
EXPERIENCE OF VITAL INVOLVEMENT . . .
NOT AN EXPERIENCE OF A PRIVATE REFER-
ENCE OF MEANING, BUT SHARING A DIMEN-
SION OPEN TO ALL HUMAN BEINGS."
(HESCHEL, 1965, p. 79)

During the past decade a series of studies initiated by
Kamiya (1968) has shown that people can discriminate
their brain states. These studies use electrical signals to
indicate brain function and recordable behaviors as meas-
ures of psychological state. A subject readily acquires the
ability to discriminate the occasions when his brain is giving
off alpha rhythms from those when his brain's electrical
activity is desynchronized. An interesting incidental finding
in these studies has been the fact that when Zen and Yoga
procedures accomplish their aims, subjects can attain the
alpha brain rhythm state at will. Kamiya's training
procedures can and are being used as a short cut to Nirvana.

More specific are some recent experiments of Libet
(1966) that have explored a well-known phenomenon.
Since the demonstrations in the late 1800's by Fritsch and
Hitzig (1870) that electrical stimulation of parts of man's
brain results in movement, neurosurgeons have explored its
entire surface to determine what reactions such stimulations
will produce in their patients. For instance, Foerster (1936)
mapped regions in the postcentral gyrus which give rise to
awareness of one or another part of the body. Thus sensa-
tions of tingling, of positioning, etc. can be produced in the
absence of any observable changes in the body part experi-
enced by the patient. Libet has shown that the awareness
produced by stimulation is not immediate: a minimum of a
half second and sometimes a period as long as five seconds

elapses before the patient experiences anything. It appears that the electrical stimulation must set up some state in the brain tissue and only when that state has been attained does the patient experience.

What do we know about the organization of these brain states apparently so necessary to awareness? They display some curious properties. One would expect that when the brain rhythms which are correlated with the subject's report are disrupted, the behavioral functions would also be interfered with. This is not the case. Focal epileptic discharge in the postcentral gyrus (Stamm and Warren, 1961) and elsewhere, unless it becomes pervasive and takes over the function of a large part of the brain, does not seriously disrupt awareness. I have densely scattered epileptic lesions in various areas of the nonhuman primate brain in a series of carefully carried out experiments and found that despite the electrical disturbance produced, problem-solving ability remains unimpaired provided the ability had been acquired before electrical seizure discharge began (Kraft, Obrist and Pribram, 1960; Stamm and Pribram, 1960; Stamm and Pribram, 1961). (The acquisition of appropriate performances after the discharges become established is, however, slowed approximately fivefold.)

In short, the brain state necessary to awareness appears to be resistant to being disrupted by local damage provided this damage is not overly extensive. An estimate of the limits on the extent to which disruption can take place without undue influence on the state comes from experiments involving brain tissue removals. Some 85% (or in some experiments even more, Galambos, Norton and Frommer, 1967; Chow, 1970) of a neural system can be made ineffective without seriously impairing the perform-

ances dependent on that system (Lashley, 1950). What sort of state is it that can function effectively when only 10 or 15' of it remains and all of what remains need not be concentrated in one location?

The answer is that the effective units of the state must be distributed across the tissue involved. Each unit or small cluster of units must be capable of performing in lieu of the whole. Until very recently it was difficult to conceive of such a mechanism.

But just as information processing by computer is an aid in conceptualizing the way in which coding operations are hierarchically constructed, so another engineering domain helps us to understand the problem of the "distributed" state. This domain is called optical information processing (van Heerden, 1968) because optical systems work this way; or, holography, because each part of a recorded state can stand in for the whole (Leith and Upatnicks, 1965).

The essential characteristic of a holographic state is the encoding of the relation among recurrences of neighboring activities. This is known technically as a spatial phase relationship. In optics, ordinary pictures encode only the intensity of illumination at any location; a hologram encodes spatial phase in addition.

Holograms have many properties of interest to the brain scientist. Foremost of these is the fact that information is distributed in the holographic record. Thus one can take a small part of the hologram and reconstruct from it an image in most respects the same as that reconstructed from the whole record. Second, a great deal of information can be stored in one hologram. Several major companies (IBM, RCA) have been able to encode well over a million bits in a square centimeter. Third, an entire image can be recon-

structed from a hologram when illumination is reflected from one feature or part of the scene originally recorded. This is the property of associative recall.

Holograms were first constructed mathematically by Dennis Gabor (1949, 1951) and crude reproductions were achieved. Later they were improved immensely by illuminating the object with a laser beam. Because of the similarity of properties of the optical hologram and the
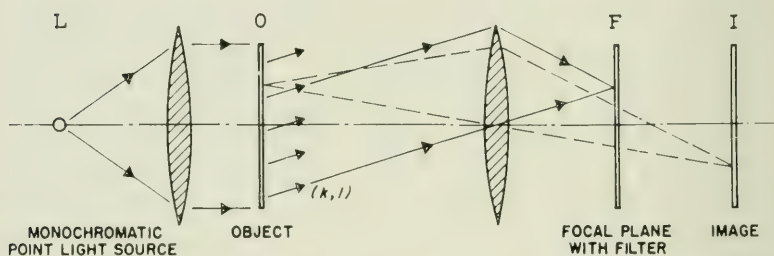

Fig. 1. The information to be stored is originally present on a transparent slide in the object plane O. It is illuminated by parallel light from a coherent light source L, like a laser beam. Consequently, in the image plane I one will see an image of the transparent object, faithful within the limitations of the optical system. We now expose a photographic plate, not in I, but in the focal plane F, to the light diffracted by the object. This plate, after exposure, is developed and a positive is made of it, which is put back in F. This filter, which has a transmission in each point proportional to the original light intensity, is called a hologram.

facts about the brain reviewed in the passages above, I have suggested that one important encoding process in the brain follows the mathematical rules of holography (Pribram, 1966). My laboratory is now working on the problem of just how the hologram is realized in neural tissue (Pribram, 1969a).

The neural hologram is a state in which information is encoded in such a way that images can be constructed.

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Although images are evanescent, they occur. Although they cannot be directly communicated, they exist. At least three types of images can be discerned subjectively, however, and for each a separate neural system has been identified. Images constructed by the operations of the classical sensory systems refer to events external to the organism (Pribram, 1966); images constructed by the operations of the limbic forebrain monitor the world within (Pribram, 1967a; Pribram, 1970); and, images constructed by the brain's motor mechanisms structure the achievements an organism aims to accomplish (Pribram, et al., 1955-56; Pribram, 1971). I want now to take a look at these motor mechanisms, for without them behavior could not occur and we could never make our images meaningful.

The Motor Mechanism and Acts

Neuroscientists have engaged in a century-long controversy regarding the functions of the motor cortex of the brain. The view common to all protagonists has been that this tissue serves much as does a keyboard upon which the remainder of the brain—or the mind—constructs the melodies to be executed by muscles as behavior (Sherrington, 1906). What has been controversial is the nature of the keyboard. Does it encode, i.e. contain a representation of, individual muscles or even parts (Woolsey, Chang and Bard, 1947; Bucy, 1949); or, does the keyboard encode movements, spatial and temporal combinations of muscle contractions, much as do the more complex controls of an organ which encode chords, timbre, etc. (Walshe, 1948; Lashley, 1921)?

Some years ago I set out to see for myself where I stood in this controversy. I repeated some of the classical experiments and performed others. The results were surprising and I was unable to understand them fully until very recently when additional data from other laboratories became available.

The first surprise came with the discovery that sensory nerves from both skin and muscle send signals to the motor cortex by pathways no more circuitous than those by which such signals reach sensory cortex (Malis, Pribram and Kruger, 1953). If the motor cortex were indeed the final common path for cerebral activity, a funnel, what business has it to be informed so directly from the periphery? The

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problem was compounded by a series of reports of experiments analyzing the organization of peripheral motor control which appeared about this time (Granit, 1955; Granit and Kellerth, 1967; Kuffler and Hunt, 1952). The results of these experiments showed that one-third of the fibers leaving the spinal cord destined for muscle end in muscle receptors and have, under the experimental conditions, no immediate influence on muscle contraction. What happens when these fibers (called the γ system because they are the smallest in diameter) are stimulated electrically is that a
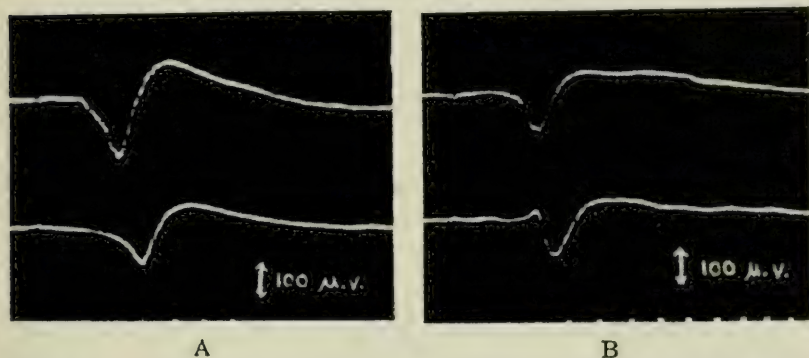
FIG. 2. A. Cortical response evoked by stimulation of superficial peroneal nerve. Upper trace in the postcentral "sensory" cortex; lower trace in the precentral "motor" cortex. Time: 10 msec. B. Same as A except that stimulus was applied to posterior tibial nerve. Note that the response in the "motor" cortex is practically identical to that in the "sensory" area.
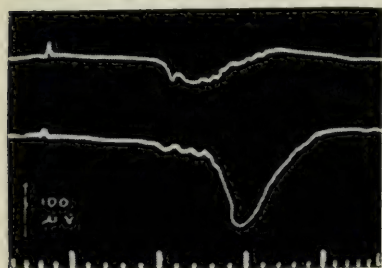

FIG. 3. These responses were obtained on sciatic stimulation after complete resection of cerebellum plus additional resection of cortex of both postcentral gyri. Upper trace, postcentral exposed decorticated white matter; lower trace, precentral cortex. Time: 2 and 10 msec. This indicates that the responses shown in Fig. 2 do not traverse the sensory cortex or the cerebellum on the way to the "motor" cortex.

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change is produced in the signals going to the spinal cord from the muscle receptors. Until these experiments were reported it had been thought that the signals from the muscle receptors accurately reflected the states of contraction or relaxation of the muscles. Now it became necessary to take into account the fact that messages from the central nervous system could influence the muscle receptors independent of any changes produced in the muscle.

The results of both these sets of experiments spelled the end to a simple stimulus-response model of how the nervous system controls behavior (Miller, Galanter and Pribram, 1960). At the periphery the reflex arc became an untenable fiction; at the cortex the keyboard had to give way to some more sophisticated conception.

The second surprise regarding the motor mechanism came with the discovery that I could remove huge amounts of motor cortex with very little impairment of muscle function (Pribram, et al., 1955-56). Neither individual muscle contractions nor any particular movements were seriously altered by the surgery. Yet something was amiss. Certain tasks were performed with less skill despite the fact that slow motion cinematography showed the movements necessary to perform the task were executed without flaw in other situations. My interpretation of this finding was that behavioral acts, not muscles or movements, were encoded in the motor cortex. An act was defined as an achievement in the environment that could be accomplished by a variety of movements which became equivalent with respect to the achievement. Thus a problem box could be opened by use of a right or left hand; amputees have learned to write with their toes. Encoded in the motor cortex are the determinants of problem solution and of writing—not the particular movements involved in the performance.

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What I could not fathom at the time was how the determinants of an act could be encoded. Two experiments have recently helped to clarify my perplexity. One was performed by Bernstein (1967) in the Soviet Union. Bernstein photographed people clad in black leotards carrying out preassigned tasks against black backgrounds. Patches of white were attached to the leotards at the locations of major joints. Examples of the tasks are hammering a nail and running over rough terrain. Cinematography showed only the white patches, of course. These described a running wave form which could be analyzed mathematically. From his analysis Bernstein could predict within 2 mm. where the next movement in the action would terminate—where the hammer blow would fall, what level the footsteps would seek. It became obvious that if Bernstein could make such a calculation, the motor cortex could also do it. Interestingly, the equations Bernstein used were the temporal equivalent of those which describe the hologram.

The second experiment gives a clue as to which determinants of acts are encoded. Evarts (1967) impaled cells in the motor cortex of monkeys with fine electrodes and recorded the activity of these cells while the monkey pushed a lever. Different weights were attached to the lever so that greater or lesser force had to be exerted by the monkey in order to accomplish the task. Evarts, to his surprise, found that the activity of the cortical neurons from which he was recording varied not as a function of the length or stretch of the muscles used to push the lever but as a function of the force needed to perform the task. Apparently what is encoded in the motor cortex is a representation of the field of forces describing the conditions necessary to achieve an action.

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Now the earlier experimental results began to make sense. The motor mechanism resembles a set of thermostats rather than a keyboard (Merton, 1953). At the periphery the receptors are subject to a dual influence: they are sensitive to muscle tension, which reflects the force exerted on the muscle, and they are sensitive to signals from the central nervous system by way of the γ fibers. This is much like the sensitivity of the thermocouple in a thermostat which is composed of two pieces of metal separated when cool but which make contact with each other by expanding when warmed. In addition to the sensitivity to temperature change the size of the gap between the pieces of metal can be varied by the little wheel at the top of the thermostat—i.e. the device can be set to be more or less sensitive to heat. There is by now a large body of evidence that the γ motor system works by setting the muscle receptor's sensitivity to changes in muscle tension (Mettler, 1967). There is also a great deal of evidence that much of the brain's control over muscle function is performed by making changes in set, in biasing the γ system, and not in making muscles move directly. Note that the setting device of the thermostat is calibrated for temperature, that it has encoded on it the information necessary to control the activity of the furnace to reach the goal set for it and that this goal can be met over a wide range of changes in the temperature of the environment. Note also that the furnace need not display any fixed rhythm of on and off—this rhythm will vary with the environmental exigencies. In the same manner, the brain's motor mechanism can encode the set points, the information necessary to achieve certain acts. The brain need not keep track of the rhythms of contraction and relaxation of individual muscles necessary to achieve an act any more than the thermostat needs to keep track of the turnings on and off of the furnace.

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The encoding problem is immensely simplified—only end states need to be specified. As already noted these can be computed by extrapolation from holographic-like equations that summarize the sequence (repetitions) of forces (muscle tension states) exerted.

This is the manner in which the brain achieves acts. But we are not yet arrived at meaning. Acts can be stereotyped, routine. They can be made necessary by environmental change, necessary merely to maintain the organism's equilibrium in the face of such changes. No, there is more to meaning than just action, as there is more to meaning than just imaging. Meaning is derived when acts intend (from the Latin *intendere*, to stretch toward), that is, reach out to, thus impaling otherwise evanescent images and keeping them from slipping away. The brain makes this possible by constructing signs and symbols.

Signs and Symbols: Association or Differentiation?

Much of my own research on nonhuman primates has been devoted to the problem of how the brain makes possible signs and symbols. For many years I questioned whether, in fact, nonhuman primates could construct signs and symbols but my doubts have now been resolved by work with two chimpanzees, one studied by the Gardners (1969) at the University of Nevada and one by Premack (1970) at the University of California at Santa Barbara. The Nevada chimpanzee named Washoe (after the county in which Reno is located) has been taught to communicate using a sign language devised for the deaf and dumb. Earlier attempts to set up a rich communicative system between chimpanzee and man had failed. The Gardners felt that this failure was due to the limitations of the chimpanzee vocal apparatus and therefore decided to use a gestural system instead. The system chosen, American Sign Language, has the added feature that it is a relatively iconic rather than a phonetic system, thus much less complex in its structure than is human speech.

Washoe has learned to use approximately 150 signs. She can string two or three signs together but not in any regularly predictable order. Comparison with deaf human children of comparable age shows marked differences in the way in which gestural signs are used—but more of this later. The point here is that sign making is possible for the nonhuman primate.

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The Santa Barbara chimpanzee, Sarah, is being trained by an entirely different method to an entirely different purpose. Premack has taken operant conditioning methods and applied them to determine just how complex a system of tokens can be used to guide Sarah's behavior. Experiments performed in the 1930's had already shown that chimpanzees will work for tokens—in fact a chimpomat had been constructed for use with poker chips. The chimpomat was an outgrowth of the delayed response task, the indirect form of which uses a temporary token to indicate where a piece of food (a reinforcer) is to be found subsequently. The delayed response task had been devised to determine whether animals and children could bridge a temporal gap between a momentary occurrence and a later response contingent on that occurrence. The bridge, which animals and children can construct, has been variously conceptualized in terms of "ideas," "memory traces," "short term memory organization," etc. Premack's chimpanzee has demonstrated that behavior dependent on tokens is not only possible but that hierarchical organizations of tokens can be responded to appropriately.

In all of these experiments the crux of the problem is that the token does not call forth a uniform response. Depending on the situation, that is, the context in which the token appears, the token must be apprehended, carried to another location, inserted into a machine or given to someone, traded for another token or traded in for a reward. Or, as in the original delayed response situation, the token stands for a reward which is to appear in one location at one time, another location at another time.

I shall use the term "symbols" to describe these context dependent types of tokens to differentiate them from "signs" which refer to events independent of the context in which

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they appear. (This distinction is consonant with that made by Chomsky [1963]. "Formal Properties of Grammars," and is used here to indicate that the primordia of the rules that govern human language are rooted in what are here called "significant" and "symbolic" processes.) There is now a large body of evidence to show that the cortex lying between the classical sensory projection areas in the posterior part of the brain is involved in behavior dependent on discriminating signs and that the frontal cortex lying anterior to the motor areas is involved in performances dependent on symbolic processes.

The surprise came when experiments were devised to show how these parts of the brain worked in determining sign and symbol. The ordinary view is that progressively more complex features are extracted or abstracted from information relayed to the projection areas: the simpler extractions occur in the projection areas *per se,* more complex abstractions demand relays beyond this primary cortex to adjacent stations where associations with information from additional sources (e.g. the primary projection areas) are made available (Hubel and Wiesel, 1965). Unfortunately for this view there is a good deal of experimental evidence against it.

Most direct is the fact that if progressive cortico-cortical relays are involved in the ability to utilize signs and symbols, then removals of these relays should impair the ability. This is not the case. The posterior and frontal cortices specifically concerned in sign discrimination and in delayed response lie some distance from the primary sensory and motor areas. Complete removal of the tissue that separates the primary areas from those involved in discrimination and delayed response does not permanently impair the performance of these tasks (Lashley, 1950; Chow, 1952; Pribram,
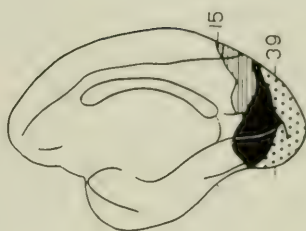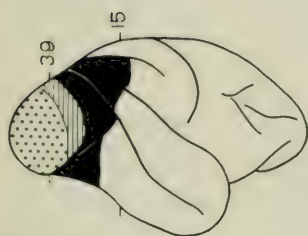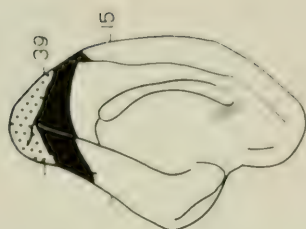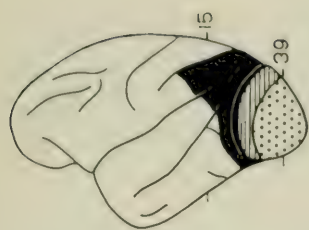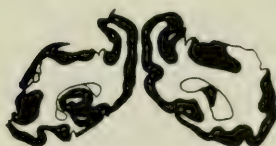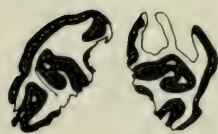
Fig. 4. Diagrammatic reconstruction of the brain after an essentially complete lesion of the peristriate cortex. Representative cross sections are shown by number indicating placement on brain diagram. The monkey from whom this brain was taken retained a visual discrimination habit perfectly.

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Spinelli and Reitz, 1969). Ergo, cortico-cortical "abstractive" relays cannot be the mechanism at issue.

Two possibilities remain to explain the involvement of those cortical areas remote from the primary projection zones in discrimination and delayed response behavior. Information may reach these areas by routes independent of those that serve the primary projection cortex. This possibility is being actively explored in several laboratories. In the rhesus monkey, however, there is already evidence that these independent routes do not play the desired role: destruction of the pathways does not lead to a deficit in the performance of discriminations or delayed response (Chow, 1954; Mishkin, 1969).

The third possibility is one that I have been seriously exploring for the past decade and a half (Pribram, 1958a). This alternative holds that sign and symbol are constructed by a mechanism that originates in the cortex and operates on the classical projection systems in some subcortical location. Thus the effects of the functioning of the cortex involved in signing and symbolizing are conceived to be transmitted downstream to a locus where they can preprocess signals projected to the primary sensory and motor cortex.

A good deal of evidence has accrued to this third alternative. Perhaps most important is the fact that a large portion of the pathway relays within the basal ganglia, motor structures of the motor mechanism of the brain (Reitz and Pribram, 1969). Sign and symbol manipulation thus involves the same brain structures that are used by the organism in the construction of acts. The suggestion that derives from these anatomical facts is that signifying and symbolizing are acts, albeit acts of a special sort.

There is, of course, a difference in the neuroanatomy involved in signifying and that involved in symbolizing. This
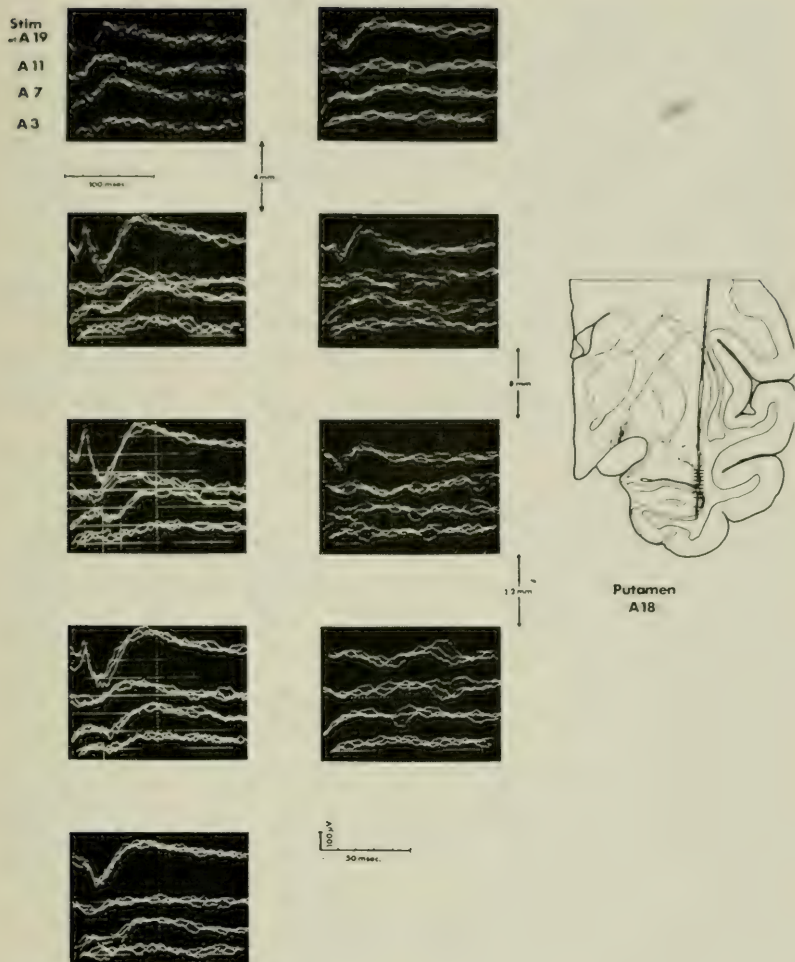
FIG. 5. Responses evoked by stimulation of the part of the temporal lobe in-volved in vision. Note tracts passing through the putamen, one of the major motor structures in the brain. Horizontal marks indicate the location of the tip of the recording electrode from which the response was photographed.

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difference, as well as the behavioral analysis of the tasks involved, tells a good deal of what these behavioral processes are all about. The pathways for signifying influence the primary sensory systems. Connections have been traced by electrophysiological techniques as far peripheral as the retina (Spinelli, Pribram and Weingarten, 1965; Spinelli and Pribram, 1966) and the cochlear nucleus (Dewson, Nobel and Pribram, 1966), for instance. The connections important to the symbolic process have not as yet been determined as fully, but a good deal of the evidence points to involvement with the limbic systems structures on the innermost boundary of the forebrain (Pribram, 1958b).

This connection between limbic and frontal lobe function demands a word or two. Removal of tissue in these systems does not impair sign discrimination but does impair performance on such tasks as delayed alternation (Pribram, et al., 1952; Pribram, et al., 1966; Pribram, Wilson and Connors, 1962), discrimination reversal (Pribram, Douglas and Pribram, 1969), shuttle-box-avoidance (Pribram and Weiskrantz, 1957) and approach-avoidance, commonly called "passive" avoidance (McCleary, 1961). In all of these tasks some conflict in response tendencies, conflict among sets, is at issue. The appropriate response is context (i.e. state) dependent and the context is varied as part of the problem presented to the organism. Thus a set of contexts must become internalized (i.e. become brain states) before the appropriate response can be made. Building sets of contexts depends on a memory mechanism that embodies self referral, rehearsal or, technically speaking, the operation of sets of recursive functions. (The formal properties of memory systems of this type have been described fully by Quillian, 1967.) The closed loop connectivity of the limbic systems has always been its anatomical hallmark and makes

an ideal candidate as a mechanism for context dependency (Pribram, 1961; Pribram and Kruger, 1954).

As an aside, it is worth noting that much social-emotional behavior is to a very great extent context dependent. This suggests that the importance of the limbic formations in emotional behavior stems not only from anatomical connectivity with hypothalamic and mesencephalic structures but also from its closed loop, self-referring circuitry. It remains to be shown (although some preliminary evidence is at hand [Fox, et al., 1967; Pribram, 1967b]) that the anterior frontal cortex functions in a corticofugal relation to limbic system signals much as the posterior cortex functions to preprocess sensory signals.

Thus signs and symbols are made by the brain's motor mechanism operating on two classes of images—in the case of signs those that encode sensory signals and in the case of symbols those that monitor various states of the central nervous system. Signs are codes invariant in their reference to events imaged—their meaning is context free. The meaning of symbols, on the other hand, is context dependent and varies with the momentary state induced in the brain by the stimulation. Both signs and symbols convey meaning, make possible a temporal extension of otherwise momentary occurrences.

Man shares the meaning conveyed by sign and symbol with nonhuman animals. This form of meaning, though perhaps more highly developed in man than in other animals, is not what makes him peculiarly human. Our search for man's unique thrust to make all his experiences and encounters meaningful needs to proceed to yet another level of complexity of encoding: only man makes propositions and reasons with them.

Propositions and Reasoning: Using Signs Symbolically and Symbols Significantly

"MAN MAY, INDEED, BE CHARACTERIZED AS A SUBJECT IN QUEST OF A PREDICATE, AS A BEING IN QUEST OF A MEANING OF LIFE, OF ALL LIFE, NOT ONLY OF PARTICULAR ACTIONS OR SINGLE EPISODES WHICH HAPPEN NOW AND THEN." *(HESCHEL, 1965, p. 54)*

A proposition is a sentence. It is made up of nouns and a predicate. Nouns are derived from signs; nouns can be conceived as signs used in sentences. Verbs are not so easy to characterize. Most verbs are also derived from signs; verbs indicate actions instead of things. Adjectives and adverbs also display this property of signification. Thus cow, green, grass, run, chew, stand, trough, drink, water, are all signs depicting events and occurrences. Only when used in sentences do these signs become nouns, verbs, adjectives and adverbs. What then makes a sentence?

Sentences are codes constructed by the mechanism of predication. My hypothesis is that predication is a symbolic process, i.e. it places linguistic signs into a context dependent frame. Predication depends on the verb "is" in its various grammatical constructions and according to my hypothesis all basic sentences are explicitly or implicitly of the form "X *is* Y."

As a corollary, predication is conceived to be a statement of belief. (See Ayer, 1946, pp. 7-15 and 91-93, for similar views.) The maker of a proposition is communicating his belief with regard to a relationship among signs. Thus negation, qualification and the like are part of predication. The sentence "the boy runs" is therefore a shorthand statement of the sentence "the boy is running" and indicates certainty

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on the part of the speaker. "I believe the boy is running"; "I think the boy is running"; "the boy may or may not run" are all qualifiers on the certainty with which the proposition is held. It is this process of making statements of certainty of belief that is unique to man and provides the thrust toward making experiences and encounters meaningful.

Propositions power meaning by introducing flexibility into the relationship among signs. A new level of coding emerges, the best formal example of which is the alphabet. Each letter is a linguistic sign, a context-free indicator that can be used as such—for instance, in organizing a dictionary. The symbolic use of the alphabet, on the other hand, provides an infinite richness of meaning through combinations of the self-same letters where context dependent relationships now become paramount. Thus "tap" and "pat" have different meanings.

Man not only uses linguistic signs symbolically, he uses linguistic symbols significantly. This he does when he reasons. He takes a context dependent linguistic symbol and for the duration of a particular purpose assigns to it a context-free meaning. This is accomplished by making explicit a set of rules governing the relationship among linguistic symbols "for the duration." The set of rules is, of course, a set of propositions. Algebra is probably the most familiar formal example of reasoning.

The point at issue is that though animals make signs and symbols, only man appears to use linguistic signs symbolically in making propositions and linguistic symbols significantly in reasoning. What then is different about man's brain that makes possible a reciprocal interaction between sign and symbol?

The common answer to this question is that man's brain is characterized by its massive cortico-cortical connectivity

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(Geschwind, 1965). This connectivity is conceived to be quantitatively, not qualitatively, different from that of non-human brains. But as we have already seen, the postulated transcortical relay mechanism of sign and symbol construction does not come off well when examined in the light of experimental evidence obtained with nonhuman primates. Instead, signs and symbols are found to be made by virtue of a mechanism that involves cortico-*sub*cortical connections that relay in structures hitherto conceived to be motor in function. Thus if man's special capability is due to his brain's cortico-cortical connectivity, this difference is qualitative not just quantitative.

The issue is an important one. If, in fact, the cortico-cortical connectivity of man's brain proves to be the source of his power of propositional language and reasoning, we have an answer to the question of what makes man human. A great deal is being made today of this cortico-cortical connectivity in terms of the "disconnection" syndromes that result in a variety of aphasias and agnosias. But data from the clinic are not always easy to evaluate and misinterpretation due to unqualified preconceptions can readily occur.

I have some misgivings about the validity of the common view that cortico-cortical connections are responsible for man's human capabilities. I cannot now fully spell out these misgivings because they are intuitive and constitute the questions directing my research plans for the immediate future. But a few points can be made. Obviously the roots of the misgivings lie in my experience with nonhuman brains. Initially the cortico-cortical hypothesis seemed self-evident. Only when experimental result after experimental result disconfirmed the hypothesis was I driven to search elsewhere to make sense of the data. However, this is not all. The cortico-cortical connection hypothesis implies that informa-

tion is transmitted by the connections. The largest bundle of connecting fibers, and one that has grown considerably in size when man is compared to monkey, is the corpus callosum which connects the two hemispheres. Yet this increase in the connectivity between hemispheres in man has led to hemispheric specialization, each hemisphere serving widely different functions. The connections seem to make it possible for the hemispheres to go their separate ways to a large extent rather than to duplicate each other as they do in nonhuman mammals (Pribram, 1962; Young, 1962).

Objections to this view of the functions of the corpus callosum immediately come to mind as a result of Sperry's (1964) fascinating split-brain patients. Sperry demonstrates that each hemisphere can be shown to control awareness independent of the other hemisphere once the callosum is cut. He infers from this that separate consciousnesses, separate minds, exist in one head in these patients. The assumption underlying this inference is that ordinarily consciousness is of a piece and that we are always single-minded. I challenge this assumption. Single-mindedness is an achievement that often demands considerable effort whether one is studying, listening during a conversation, or driving an automobile. Sperry's patients are not unique in being of two minds on occasion.

Other evidence that gives rise to my misgivings with the connectionist hypothesis comes from unilateral brain ablations that produce symptoms which are alleviated by further brain ablation. Thus unilateral ablations of the frontal eyefields in monkey and man result in a temporary disregard of stimuli in the contralateral visual field (Kennard, 1939; Pribram, 1955). Such disregard does not occur if the lesion is bilateralized. Also, unilateral occipital lobectomy in the cat results in a homonymous hemianopia which is relieved

when the ipsilateral optic colliculus is removed (Sprague, 1966).

These are but straws in the wind but they prevent me from obtaining too easy and early a closure on the problem of what makes man human. In order that the issue can be faced squarely, however, I must offer an alternative to the cortico-cortical connection hypothesis. My alternative is that man makes meaning through signs, symbols, propositions and reasoning by way of corticofugal-subcortical connections that importantly involve the motor mechanisms of the brain. I propose that man's thrust toward meaning derives from the fact that his brain's motor mechanisms are better developed than those of animals. These motor mechanisms are not to be conceived, as we have seen, merely as movers of muscles. The brain's motor mechanisms are devices that set the sensitivity of receptors and afferent channels, not just of muscle receptors but those of all receptors (including eye and ear) as well. Changes in setpoint regulate awareness and behavior. The changes and their results can relatively simply be encoded in brain tissue and thus serve as guides subsequently.

Conclusion

*"THINKING IS LIVING AND NO THOUGHT IS
BRED IN AN ISOLATED CELL IN THE BRAIN."
(HESCHEL, 1965, p. 81)*

The implications for education of this propensity of the
brain for encoding and recoding its sensitivities are obvious.
In order to make information meaningful we must allow
pupils to encode in terms of their own sensitivities which
are not necessarily ours. They must be given the opportunity
to repeat the information given in such a way that it be-
comes encoded in a context which makes meaning for them.
They must be encouraged to remake what we give them in
their own image.

This is not as difficult as it sounds. As already noted, even
young children who are deaf use signs differently from the
way Washoe the chimpanzee uses signs. Human children
spontaneously make propositions, their language is produc-
tive (Jakobsen, 1966). All neural tissue is spontaneously
active, nerve cells beat out electrical signals on their own
throughout life, much as does the tissue of the heart. In man
this spontaneity becomes organized early on so that he pro-
duces propositions, makes sentences. And then he begins to
play with these sentences, recoding them into different forms
and reasoning with them. Each new batch of teenagers
attests to the human proclivity for productively recoding
what is given. Why not utilize this marvelous capacity to
advantage in our educational effort?

To summarize briefly: man's brain is different in that it
makes imperative the productive use of linguistic signs
symbolically and linguistic symbols significantly. The flexi-
bility derived from this difference is immense. Given the

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power of this flexibility man codes and recodes for fun and profit. Every artistic endeavor, every working accomplishment depends for its effectiveness not only on the information conveyed by the theme but on the variations on that theme. Human encounter is sustained not just by an exchange of information but by an infinite variety in familiar communication. Animals use signs and symbols only in special circumstances; man productively propositions all his encounters and he reasons about all his experiences. Thus man and only man shows this thrust to make meaningful his experiences and encounters: he intends, he holds on to his images.

But this is not all. By means of the motor mechanisms of his brain man hopefully and continuously sets and resets his sensitivities so that his images can become actualized in his environment both by virtue of his own behavior and that of socially contiguous others. Man's culture expresses these hopes, this active thrust toward meaning. For to be human is to be incapable of stagnation; to be human is to productively reset, reorganize, recode, and thus to give additional meaning to what is. In short, "to be human is to be a problem." (Heschel, 1965, p. 105).

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Many important aspects of the problem of the brain's coding processes are dealt with here altogether too briefly. But the present paper will serve as a prolegomenon to a more comprehensive study which will appear under the title *Languages of the Brain: Experimental Paradoxes and Principles in Neuropsychology,* to be published by Prentice-Hall in 1971.

FORTY-THIRD
JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1973

THE ROLE OF HUMAN SOCIAL BEHAVIOR
IN THE EVOLUTION OF THE BRAIN

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THE AMERICAN MUSEUM OF NATURAL HISTORY
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JAMES ARTHUR LECTURES ON
THE EVOLUTION OF THE HUMAN BRAIN

Frederick Tilney, *The Brain in Relation to Behavior*; March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values*; April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man*; April 24, 1934

C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races*; April 25, 1935

Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders*; May 15, 1936

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Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull*; May 5, 1938

G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates*; May 11, 1939

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Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates*; May 8, 1941

George Pinkley, *A History of the Human Brain*; May 14, 1942

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Tilly Edinger, *The Evolution of the Brain*; May 20, 1948

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*Fred A. Mettler, *Culture and the Structural Evolution of the Neural System*; April 21, 1955

*Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny*; April 26, 1956

*Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man*; April 25, 1957

*David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action*; May 8, 1958

*Charles R. Noback, *The Heritage of the Human Brain*; May 6, 1959

*Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization*; May 26, 1960

Paul I. Yakovlev, *Brain, Body and Behavior. Stereodynamic Organization of the Brain and of the Motility-Experience in Man Envisaged as a Biological Action System*; May 16, 1961

H. K. Hartline, *Principles of Neural Interaction in the Retina*; May 29, 1962

Harry Grundfest, *Specialization and Evolution of Bioelectric Activity*; May 28, 1963

*Roger W. Sperry, *Problems Outstanding in the Evolution of Brain Function*; June 3, 1964

*José M. R. Delgado, *Evolution of Physical Control of the Brain*; May 6, 1965

Seymour S. Kety, *Adaptive Functions and the Biochemistry of the Brain*; May 19, 1966

Dominick P. Purpura, *Ontogenesis of Neuronal Organizations in the Mammalian Brain*; May 25, 1967

*Kenneth D. Roeder, *Three Views of the Nervous System*; April 2, 1968

†Phillip V. Tobias, *Some Aspects of the Fossil Evidence on the Evolution of the Hominid Brain*; April 2, 1969

*Karl H. Pribram, *What Makes Man Human*; April 23, 1970

Walle J. H. Nauta, *A New View of the Evolution of the Cerebral Cortex of Mammals*; May 5, 1971

David H. Hubel, *Organization of the Monkey Visual Cortex*; May 11, 1972

János Szentágothai, *The World of Nerve Nets*; January 16, 1973

*Ralph L. Holloway, *The Role of Human Social Behavior in the Evolution of the Brain*; May 1, 1973

*Elliot S. Valenstein, *Persistent Problems in the Physical Control of the Brain*; May 16, 1974

THE ROLE OF HUMAN SOCIAL BEHAVIOR
IN THE EVOLUTION OF THE BRAIN

INTRODUCTION

The presentation of this lecture has particular significance for me because only slightly more than 11 or 12 years ago as a graduate student of human evolution I discovered with great excitement the existence of the James Arthur lectures; these surely decided my fate, at least in part.

I wish to discuss some of the brain endocasts of our earliest fossil hominid ancestors and to show that the human brain has been around for quite a long time, perhaps three million years – or longer. This is somewhat of an about-face for me, for when I wrote my dissertation about 10 years ago, I regarded endocasts as so much rock or plaster, with little, if any, potential of offering evidence on the evolution of the hominid brain. I believe I have mellowed. Today endocasts are the subject of my major research effort.

My questions about the human brain are: What lines of evidence can we use to learn about it; how did it evolve to its present state; can we find something in its evolution relevant for today's societal existence?

Before I discuss these questions in detail, I wish to briefly consider my basic conclusions:

1. The usual orthodox version of hominid evolution places the evolution of the brain as a terminal phase, one that occurs after all other parts of the body, such as the hands, the trunk, the teeth, and the locomotory anatomy for bipedalism have evolved. This view is very oversimplified, if not downright incorrect, and approximates truth only if we are willing to equate brain evolution with brain enlargement. Indeed, the evidence shows that brain modification to a human pattern occurred early in human evolution, at least three million years ago.

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2. Both brain endocasts and bodily skeletal parts suggest that brain:body relationships remained fairly constant during most of human evolution, indicating an important set of selection pressures for body-size increase. This evidence also suggests that brain encephalization, as measured by Stephan's (1972) "progression indices" (related to a "basal insectivore" line), was already within the human range in the early fossil hominids. The mediating factor for increase must have been an endocrine-target tissue adjustment resulting in selection for increased delays of maturation, or prolonged growth and dependency times, important factors in any consideration of social behavior.

3. The humanly organized brain and resultant human cultural behavior have been interacting in a positive feedback manner during most of human evolution (Holloway, 1967). This feedback interaction is probably over, and unless some new radical genetic change occurs to interrupt man's present growth pattern, or a new social order that practices some form of genetic surgery comes into existence, I do not believe the human brain will show any further significant evolution in terms of size increase.

4. Brain endocasts have enormous value in the study of human evolution that extends far beyond brain-behavior correlations. They can give us information about variation, population statistics, and brain:body ratios, and therefore have importance in relating early hominid populations to ecological parameters such as biomass and growth and development.

5. Finally, we must realize that human behavior is not a recent achievement — our social behavior, our sociality has long evolutionary roots that cannot be abridged simply by cultural fiat.

Abbreviations used in the text and figures are:

ER, East Lake Rudolf
HE, Indonesian *Homo erectus*
MLD, Makapansgat, S. Africa
OH, Olduvai Gorge
OMO, Omo Valley, Ethiopia
SK, Swartkrans
STS, Sterkfontein

LINES OF EVIDENCE

DIRECT

It has long been appreciated that the only direct evidence for the study of brain evolution comes from the endocasts of our fossil ancestors (Edinger, 1929, 1949, 1964; Holloway, 1964, 1966a; Radinsky, 1967, 1970). Whether they are natural endocasts of the South African australopithecines (e.g., Taung, STS 60, Type 3, and SK 1585) or prepared in the laboratory from latex, plaster of Paris, and plasticine, they give only the most limited information about neural structure and no direct information about behavior. An endocast is simply a mold of the inside bony table of the cranium. Between the bone and the underlying brain there are three meningeal tissues of varying thickness, as well as a variably distributed amount of cerebrospinal fluid. The thick dura mater, the arachnoid space, the investing thin layer of pia mater, and the cerebrospinal fluid all "conspire" to eradicate the sulcal and gyral configurations imprinted by the surface of the cerebral cortex into the bony layer of the cranium. This "conspiracy" varies in different orders of animals; it is most severe, unfortunately, in the living and fossil species of apes and man. The reasons for this and the reasons for variation with age are not totally understood, but they are probably linked to differential growth rates of the brain and the overlying cranial bones in different regions (e.g., Hirschler, 1942; Keith, 1931).

Endocasts can be obtained from fossil cranial fragments in two ways. Natural endocasts occur when the skull is filled by fine sediments drifting through the cranial foramina, particularly the foramen magnum. The sediments may be compacted and solidified by percolating mineral solutions, resulting, in time, in a solid mass of sedimentary rock inside the skull. The skull bones may eventually erode away leaving the endocast intact. Usually the skull is preserved around the endocast, as is sometimes the case with the South African australopithecines, such as the Taung specimen, STS 60, Type 3, and the more

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recent SK 1585 (figs. 1-8). In SK 1585 I deliberately removed the already eroded bones to disclose the fine-grained natural endocast (see Holloway, 1972a for details).

Endocasts may also be made by applying liquid rubber latex to the inner cranial surface of a skull. This method has been used for most of the endocasts, including all the rest of the hominids from East Africa, Asia, and Europe. Successive layers are built up until a reasonable thickness, perhaps an eighth of an inch, is reached. The latex is cured by heat and then collapsed from the skull, either before or after stabilizing the dimensions with plaster. The external details of the cerebral cortex, as transmitted through the dura mater, will be reproduced on the surface of the latex. If the inner bony table is eroded before the endocasts are made, the details will obviously be missing.
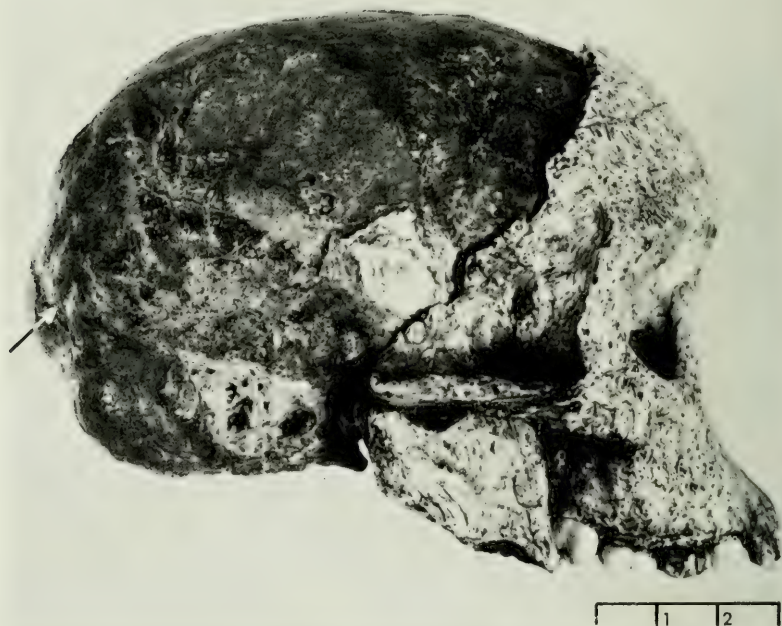

FIG. 1. Lateral view of Taung infant endocast and face positioned together. Arrow points to lambdoid suture, which is probably the most anterior extent of lunate sulcus. Scale equals 3 cm.

FIG. 2. Lateral view of Taung infant endocast. Arrow points to third inferior frontal convolution. Small portion of frontal lobe remains embedded in facial fragment. Scale equals 3 cm.

INDIRECT

Brains influence behavior, and occasionally the results of behavior become, so to speak, fossilized. Fortunately, the paleoanthropologist has lines of evidence for the evolution of the brain other than brains or endocasts. There are two sources of indirect evidence: (1) cultural products of brain and social behavioral activity, e.g., stone tools, shelters, animal remains at ancient butchering sites; and (2) skeletal components of the masticatory and locomotor systems. No indirect evidence can yet be used to demonstrate any specific changes in the brain observable at the surface. It is, however, indicative of different behavioral capabilities, which require, after all, neural com-

FIG. 3. Occipital view of Taung infant endocast. Lambdoid suture is distinct. Notice gyral curvature (shown by dotted line and arrow) immediately superior and anterior to lambdoid suture, indicating that more forward placement of lunate sulcus would not be possible. Scale equals 3 cm.

plexes to effect them. In other words, it supports the idea of brain reorganization.

The first line of indirect evidence applies, as far as we know, only to hominids. There is no evidence from the fossil record of the cultural behavioral effects in other lines of primates. The second line of indirect evidence, that is, musculoskeletal, is far more general and applies to all lines of animals, most particularly to the mammals. But what we see in the hominid fossils is rather specific, at least when compared with other fossil primates, or extant ones, for that matter. The earliest hominids show definite changes in masticatory apparatus – in the teeth, jaws, and areas of muscle attachment for the temporalis and

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FIG. 4. Lateral view of plaster replica of SK 1585, endocast from Swartkrans, South Africa. A small portion of frontal lobe is missing. Lambdoid suture obscures posterior limit of lunate sulcus. (See Holloway, 1972a.) Scale equals 3 cm.

masseter in particular. We find changes in the molars as far back as 10 to 14 million years ago in *Ramapithecus* (Pilbeam, 1969; Simons, 1961, 1964, 1969). Among the early hominids of East and South Africa there are changes in nuchal musculature related in part to advanced degrees of bipedal locomotion, which itself is corroborated by the remains of the locomotor skeleton (pelvis, lower vertebral column, limb bones such as the femur, tibia and fibula, and various bones of the foot). Even the hand bones, at least of the East African hominids, show changes in musculoskeletal structure suggestive of manipulative abilities greater than those of any fossil or living ape or monkey.

Why belabor these points? Because they show, whether or not the precentral gyrus appears on the surface of the endocast,

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FIG. 5. Occipital view of plaster replica of SK 1585 endocast. Scale equals 3 cm.

that natural selection has long been operating on behavior, favoring neural organizations capable of servicing the new musculoskeletal complexes.

This line of indirect evidence for brain reorganization need not be related only to motor or sensorimotor behavior, such as the various muscle contractions involved in bipedalism, but it must be taken to involve the whole adaptive complex (hunting, scavenging, carrying objects, and so on) in which these motor patterns are embedded and to include aspects of psychological restructuring as well. It is true that there is yet no way of comparing a gorilla endocast to that of an australopithecine or a
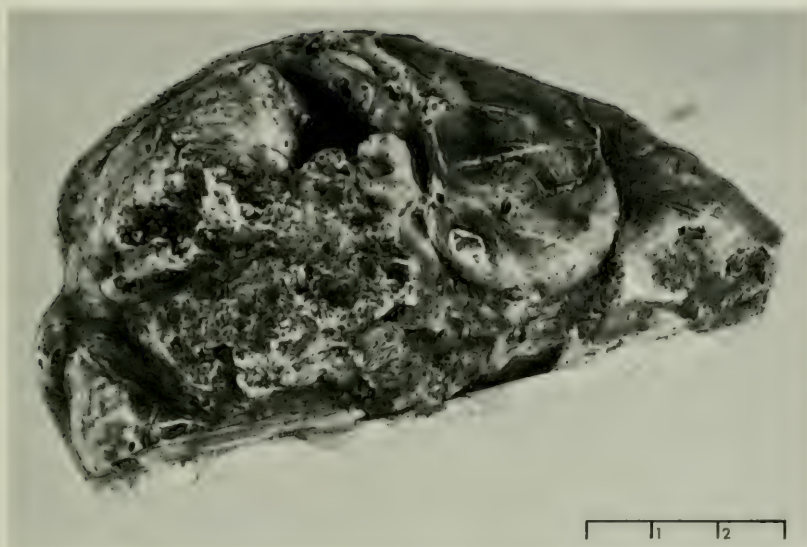
FIG. 6. Basal view of plaster replica of SK 1585 endocast. Scale equals 3 cm.

Homo sapiens to show correlated changes between brain surface features and motor behavior. Endocasts may or may not reflect important adaptive changes in behavior and structure, but by themselves they cannot indicate whether the brain evolved before or after the sensorimotor changes.

THE EVIDENCE

Evidence from which I conclude that the brain has always been an important component of human evolution is as follows:

1. Gross Morphology: Hominid endocasts show a human shape that is not found among a sample of 50 chimpanzee and gorilla endocasts. Although there can be considerable variation in endocasts of living pongids (figs. 9-16), none shows the combination of features seen on hominid endocasts. The differences are as follows:

a. The height of the brain above the cerebellar lobes is almost always greater in hominid brains. Occasionally the brain of
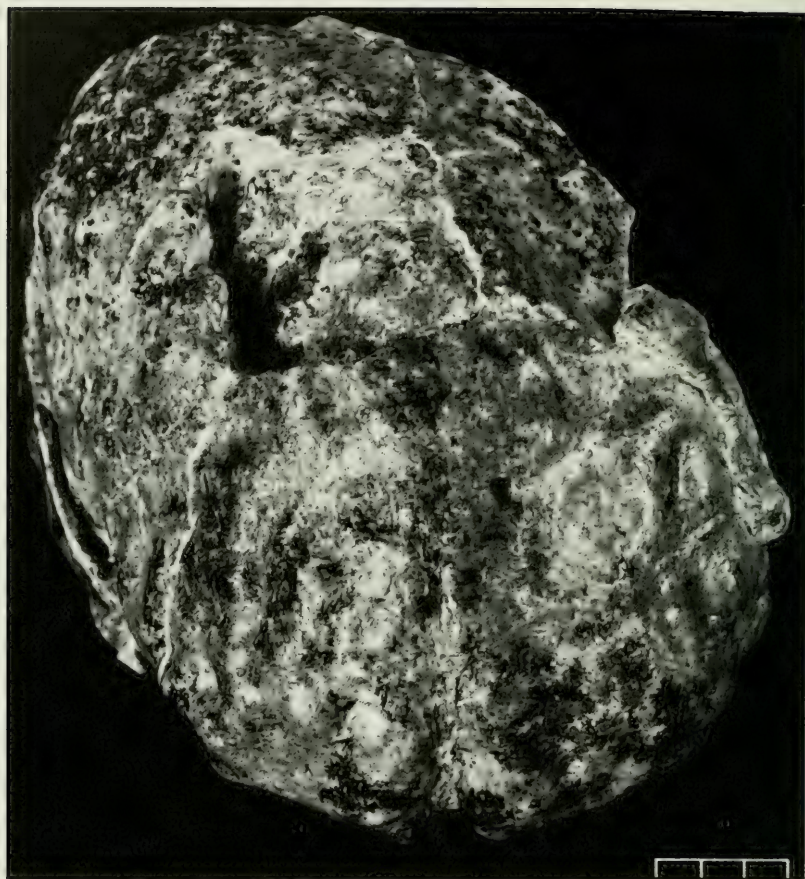
FIG. 7. Dorsal view of Type 3 endocast, a gracile australopithecine from Sterkfontein. Note double-valleyed fracture in parietal lobe, squared-off shape of frontal lobe, and suggestion of heavy gyral and sulcal relief. (See Schepers, 1946.) Scale equals 3 cm.

the pygmy chimpanzee, *Pan paniscus*, shows less flattening in height than that of either the gorilla or the chimpanzee (*Pan troglodytes* sp.) but it is not so high as that of the early australopithecines (table 1).

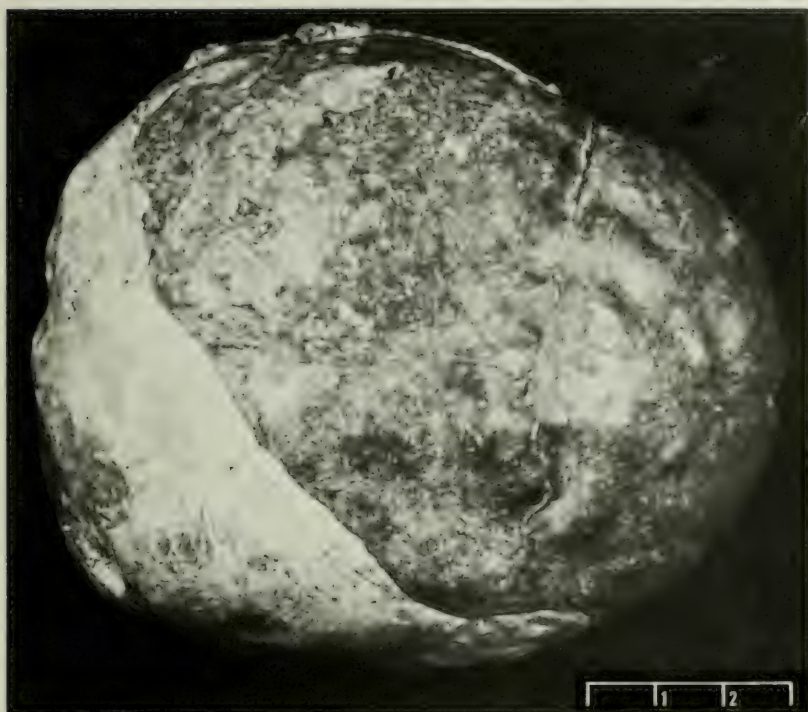b. The anterior tips, or poles, of the temporal lobes are

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FIG. 8. Dorsal view of endocast of STS 60 from Sterkfontein. Scale equals 3 cm.

distinctly more rounded and larger in hominids than in pongids (part of this is, of course, due to the different shape of the greater wing of the sphenoid and the dural sheath surrounding the tip of the lobe).

c. The orbital surface of the frontal lobe is generally angled upward, with a more pointed and pronounced beak in pongid than in hominid brain casts.

d. In pongid endocasts the position of the famous "lunate" or "simian" sulcus, which divides the primary visual cortex from the so-called parietal "association" cortex, is usually in a fairly anterior position (although less so than in cerco-pithecoids). Although only a few hominid endocasts [particularly the original Taung (1924) endocast] show the sulcus

clearly, it is definitely in a posterior, human-like position (figs. 3, 5). It is probably this feature, more than any other, that so firmly suggests cortical reorganization to a human pattern. This observation was first noted by Dart (1925), later by Schepers (1946), and was more or less verified by Sir Wilfred LeGros Clark (1947); a close examination shows no alternative position.

e. The inferior border of the temporal lobe also shows enlargement, reflected in a smaller, or more acute, angle of the petrosal cleft.

Taken together, these features form a Gestalt that is very difficult to demonstrate by linear measurements, as many physical anthropologists would wish. It is these 'Gestalten' that enable one to distinguish between pongid endocasts, such as between those of chimpanzees and gorillas, even though most measurements and indices tend to overlap.

f. Finally, it is possible that there is more sulcal and gyral development in hominid cortices, particularly on the frontal lobe, than in pongid cortices; however, this is not easily measured on endocasts and is at best an impressionistic judgment.

2. Gross Size: This parameter (or to follow Jerison, 1973, "statistic") is perhaps the crudest of all. The small absolute sizes of the australopithecine endocasts tended to deny them hominid status long after their discovery. Elsewhere I (Holloway, 1964, 1966a, 1968, 1970, 1972b) have detailed my observations on the signficance of this measurement of the brain. Some chimpanzees and most gorillas have larger brains than the early hominids (see, for example, Tobias's 1971 compilations). The range of variation in normal present-day *Homo sapiens* is from about 1000 to 2200 cc., or about as much as the total evolutionary gain from *Australopithecus africanus*, at *ca.* 450 cc., to the average value of modern *Homo sapiens* of about 1400 cc. Yet there has never been any demonstration, among living populations, of a relationship between brain size (measured either by weight or volume) and behavior. Although some human microcephalics have brain
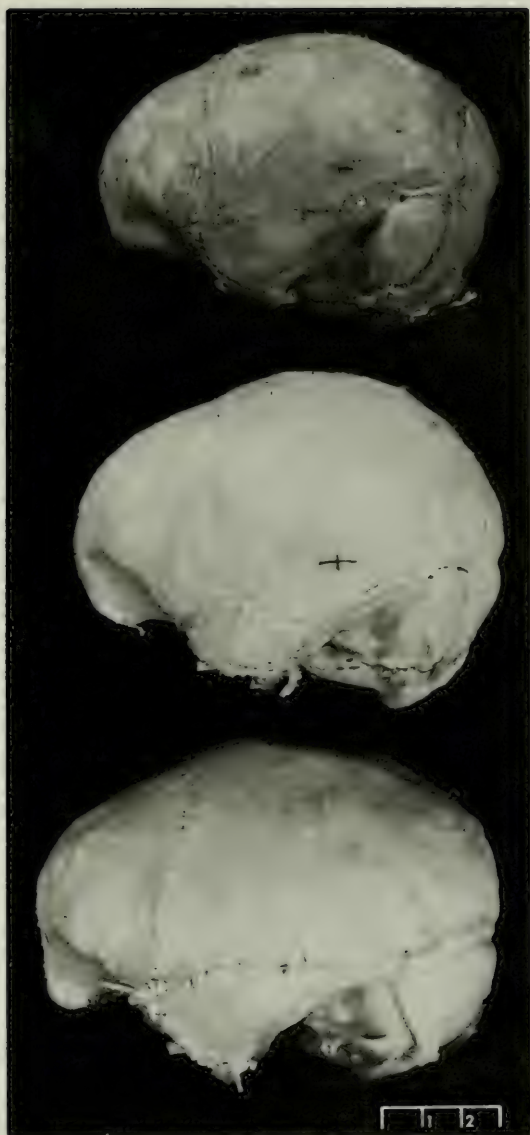
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FIG. 9. Lateral views of rubber latex endocasts of (top) *Pan paniscus*, pygmy chimpanzee, (middle) *Pan troglodytes*, and (bottom) *Gorilla gorilla*. (Rubber latex endocasts made by author from specimens belonging to the American Museum of Natural History.) (See figs. 10 and 11 for occipital and dorsal views of same specimens.) Scale equals 3 cm.

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FIG. 10. Occipital views of rubber latex endocasts of (left) *Gorilla gorilla*, (middle) *Pan troglodytes*, and (right) *Pan paniscus*. (See figs. 9 and 11 for lateral and dorsal views of same specimens.) Scale equals 3 cm.
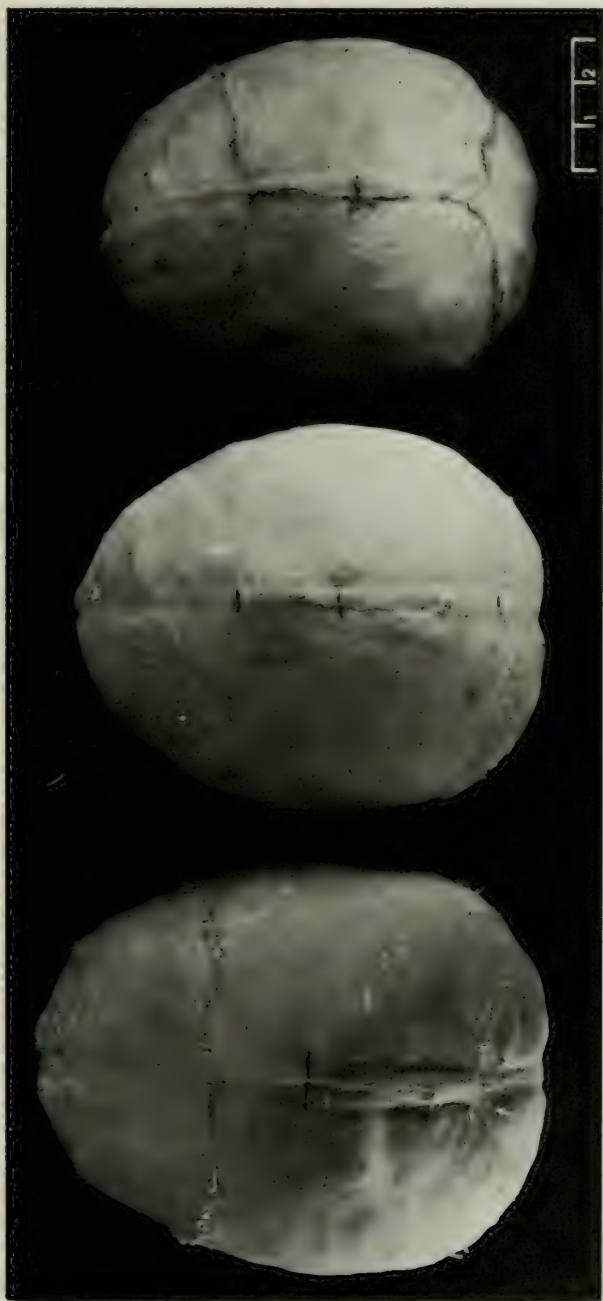
FIG. 11. Dorsal views of rubber latex endocasts of (left) *Gorilla gorilla*, (middle) *Pan troglodytes*, and (right) *Pan paniscus*. (See figs. 9 and 10 for lateral and occipital views of same specimens.) Scale equals 3 cm.
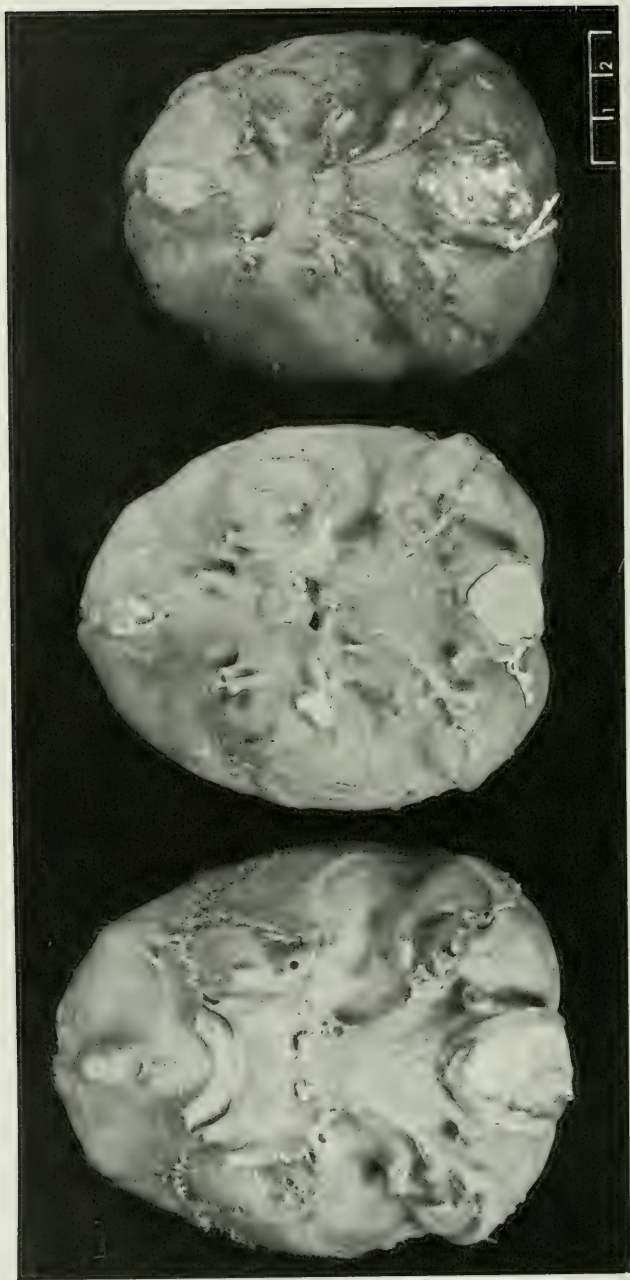
FIG. 12. Basal views of rubber latex endocasts of (left) *Gorilla gorilla*, (middle) *Pan troglodytes*, and (right) *Pan paniscus*. Scale equals 3 cm.
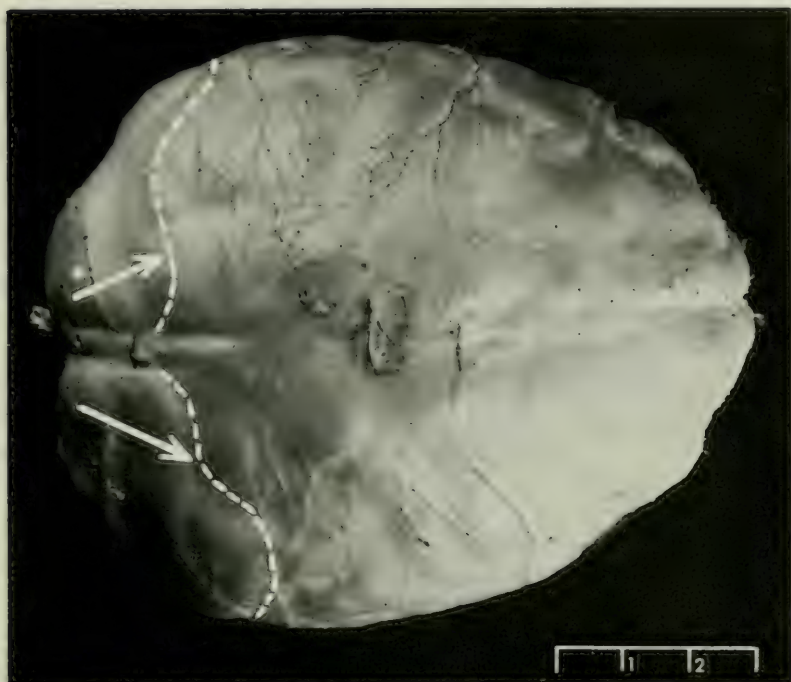
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FIG. 13. Dorsal view of endocast of different, or another *Pan troglodytes* showing excellent gyral and sulcal markings. Arrows indicate anterior limit of lunate sulcus. (Rubber latex endocast made by author from a specimen at the American Museum of Natural History.) Scale equals 3 cm.

volumes that gorillas, and perhaps a few large chimpanzees, might disdain, they do not exhibit simian behavior, but rather show the species-specific ability for symbolic language, albeit disadvantaged.

The usefulness of this crude measure of the brain lies in its statistical utilization as a parameter from which other neural measures, such as neuron size, glial/neuron ratio, neural density, and dendritic branching may be calculated. All of these variables are closely tied in with behavioral variation, although it remains for future scientists to demonstrate this unambiguously (see Holloway, 1964, 1966a, 1966b, 1968; Jerison, 1973).
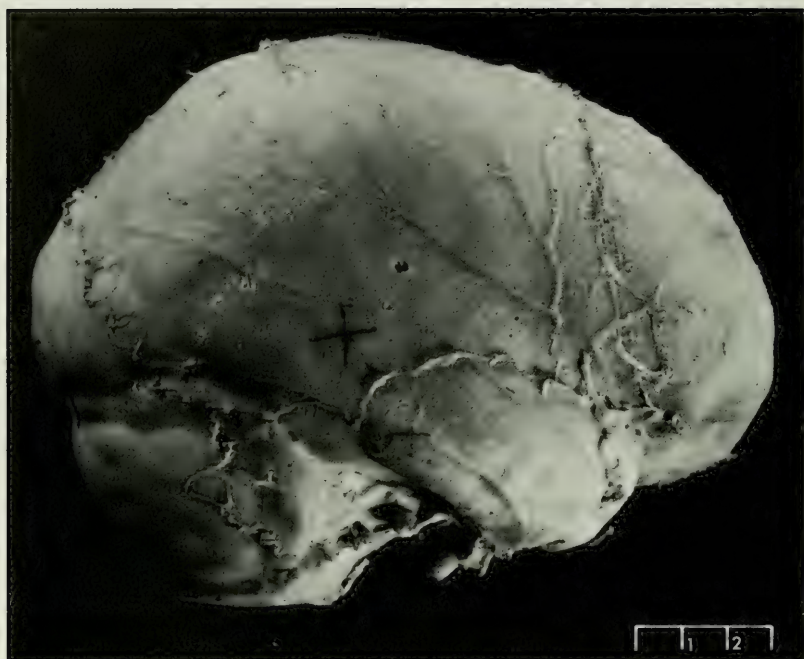
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FIG. 14. Endocast of modern *Homo sapiens*, lateral view. Note great height of cortex above cerebellum, expansion of temporal lobe in anterior and posterolateral margins, and slight slope of orbital surface on frontal lobe. (Rubber latex endocast made by author from specimen belonging to Columbia University.) Scale equals 3 cm.

Gross brain size is also related to body mass and time, and thus it can be used in combination with these other variables to give us clues about changes in growth rates during evolution in particular phyletic lines. The study of brain:body allometric relationships in different animal lines has had a long history and is a subject that is receiving considerable attention by modern scientists (see, for example, Jerison, 1973). So far, however, most of these studies have been concerned with comparisons between high-level taxa, such as between carnivores and herbivores, reptiles and birds, pongids and modern man. But if brain and body size can be measured with reasonable accuracy within a phyletic line, such as the Hominidae, the changes in allometric relationships with time can provide extremely im-

FIG. 15. Same specimen as figure 14, occipital view. Scale equals 3 cm.

portant clues to selection pressures operating on variables such as growth rates of different parts of the body, encephalization, postnatal growth, and so on, which obviously have important biological relationships with social behavior and adaptation. In other words, another significant use of gross brain size, beyond that of simply indicating overall size increase, is as a key to other relationships that may have been more concerned with selection pressures.

Unfortunately our samples for various hominid lineages are terribly small, and many specimens (e.g., the South African hominids) are not firmly dated; it is thus impossible to plot brain size against time in any accurate manner. If we could, the rates might give us some interesting clues to past selection

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FIG. 16. Same specimen as figure 14, basal view. Scale equals 3 cm.

pressures and dynamics (see Holloway, 1972b). Table 2 gives a number of newly determined endocranial capacities for various hominids. The methods used to arrive at these figures are given in the footnotes to this table.

3. Relative Brain Size and Encephalization: There appears to be a lawful relationship between brain and body size in all vertebrate taxa (see Jerison, 1973, for a thorough review of this relationship). In general, following the principle of allometry, larger-bodied animals tend to have a proportionally smaller brain weight. It is possible to plot the size of the brain against the weight of the body on double-logarithmic graph paper and to discern some reasonably straight-line relationships. Regression lines are of the general form $E = kP^y$, where E = brain weight, P = body weight, y = an exponent probably reflecting the

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relationship between volume and surface area, and k = a constant, often taken to reflect "encephalization," or the relationship between brain:body weight ratios in different animals. Plotting different orders of vertebrates on the same graph tends to give an exponent of 0.66; for closely related species the exponent usually falls between 0.20 and 0.30. Within the species, however, there seldom appears a relationship, but this is probably debatable.[1] The human brain is neither the smallest nor the largest in terms of relative size. Table 3 gives a few examples of animals with large and small relative brain weights. This table does not show, however, the range of variation within each category for brain:body weight ratios, for which few published data exist.

Using a large number of "basal" insectivores (representing the sort of primitive stock out of which the primates may have evolved), Stephan (1972) was able to construct a "basal" insectivore line, defined as $\log_{10} h = 1.632 + 0.63 \log_{10} k$. By substituting a primate's body weight in the equation (k), it is possible to solve for "h," which gives the expected brain weight of a "basal" insectivore with such a body weight. If this weight is then divided into the actual brain weight of the particular primate, an "index of progression," or measure of encephalization, results (table 4 shows a number of "progression indices" for different primates, including some fossil hominids). This last step requires making a hazardous assumption about the body weight of the fossil hominid. Nevertheless, allowing for maximal and minimal body weight, the South African gracile australopithecines fit either within the range for modern man or just below it, but always above the pongid range. This is indirect evidence for reorganization of these early hominid brains to a

[1]Very little secure data exist for large samples of healthy individuals, which requires study by more sophisticated statistical methods, such as partial correlations. To date no such study has been published, not even in the excellent article by Pakkenberg and Voigt (1964) on the Danes. I give this warning because a preliminary analysis of a partial correlational study between the variables of age, weight, body height, and brain weight suggests more of a relationship between brain and body weight than is usually recognized. I hope to publish these results in the near future, thanks to the courtesy of Dr. Pakkenberg, who has given me the original data.

human pattern, but it does not tell us whether there is a general allometric increase in overall size or whether there has been differential development of particular elements of the brain.

Still, these data are more relevant for understanding evolutionary change than are mere comparisons of gross brain size. It is a great pity that we do not as yet have a way to determine accurately the body weights of our hominid ancestors. If we did, we could plot these for particular lineages and, possibly, relate the resulting exponents to evolutionary selection pressures.

Figure 17 and table 5 show a range of possible brain:body weight relationships, based on current estimates of hominid body weights (Tobias, 1967; Lovejoy and Heiple, 1970) that might have characterized stages of hominid evolution. Interpretation of selection pressures for increasing brain size varies, depending on whether the exponents linking the fossil hominid lineages are > 1.0, 1.0, 0.66, or less. The exponent 0.66 characterizes most nonhominid mammals (Jerison, 1973),

TABLE 1
Some Crude Indices for Hominid Endocasts[a]

Specimen	Volume in Milliliters	$\dfrac{D\ arc}{L\ arc}$	$\dfrac{D\ arc}{L}$	$\dfrac{L}{H}$	$\dfrac{H^3}{V}$
Taung	404	1.13	1.48	1.41	1.41
STS 60	428	1.00	1.35	1.40	1.29
STS 5	485	1.08	1.39	1.42	1.27
OH 5	530	1.47	1.37	1.45	1.20
SK 1585	530	1.73	1.42	1.43	1.37
ER 732	506	1.06	1.42	1.48	1.13
OH 24	590	1.01	1.29	1.40	1.32
OH 13	650	1.17	1.49	1.48	1.16
OH 9	1067	1.05	1.31	1.55	1.18
OH 12	727	1.11	1.41	1.60	0.97
HE I[b]	943	1.10	1.33	1.59	1.02
HE II[b]	815	1.06	1.35	1.53	1.08
HE IV[b]	900	1.00	1.31	1.64	0.94
HE VI[b]	855	1.05	1.33	1.68	0.97
HE VII[b]	1059	1.07	1.41	1.65	0.92
HE VIII[b]	1004	0.98	1.25	1.61	1.00
ER 1470[c]	770	1.04	1.37	1.36	1.30
Omo 338s	427	1.02	1.37	1.54	1.03

TABLE 1 – (*Continued*)

Specimen	Volume in Milliliters	$\dfrac{\text{D arc}}{\text{L arc}}$	$\dfrac{\text{D arc}}{\text{L}}$	$\dfrac{\text{L}}{\text{H}}$	$\dfrac{\text{H}^3}{\text{V}}$
Pan paniscus (n = 8)					
average	325	0.99	1.33	1.46	1.04
range	284-363	0.97-1.01	1.28-1.37	1.36-1.54	0.86-1.21
Pan troglodytes (n = 29)					
average	394	0.96	1.28	1.47	1.09
range	334-474	0.88-1.01	1.20-1.34	1.39-1.59	0.95-1.23
Gorilla gorilla (n = 36)					
average	498	0.98	1.26	1.53	1.04
range	383-625	0.94-1.04	1.19-1.33	1.39-1.67	0.85-1.24
Homo sapiens (n = 4)					
average	1442	1.10	1.43	1.40	1.25
range	1324-1586	1.04-1.14	1.39-1.46	1.35-1.46	1.11-1.42

Symbols: D arc = dorsal measurement between frontal and occipital poles; L arc = lateral measurement between frontal and occipital poles; L = chord length between frontal and occipital poles; H = chord length from vertex to lowest plane of temporal lobe; V = volume.

[a]These figures clearly show that most hominid fossils (*Homo erectus* excepted) have a greater degree of cortical height relative to both length and volume than do the African pongids tested.

[b]The well-known platycephaly of the Indonesian *H. erectus* is clearly shown by the L/H value, the low D arc/L arc, D arc/L and H^3/V ratios.

[c]This specimen does not show a typical *H. erectus* pattern.

"basal insectivores," and most lower primates (Stephan, 1972). This exponent suggests an allometric increase, where brain weight increases at a smaller rate than body weight. An exponent of approximately 1.0 indicates a constant brain:body weight ratio, suggesting selection pressure for brain weight to match body weight. An exponent greater than 1.0 suggests selection pressures for brain weight greater than that for body weight.[1]

[1]Of course, an exponent of 1.0 in hominids does mean an increase in brain size when compared with either a "basal" insectivore or vertebrate line where the exponent is about 0.66.

TABLE 2
Endocranial Volumes of Reconstructed Hominid Specimens

Specimen	Taxon	Region	Endocranial Volume in Milliliters	Method[a]	Evaluation[b]
Taung	*A. africanus*	South Africa	440[c]	A	1
STS 60	*A. africanus*	South Africa	428	A	1
STS 71	*A. africanus*	South Africa	428	C	2-3
STS 19/58	*A. africanus*	South Africa	436	B	2
STS 5	*A. africanus*	South Africa	485	A	1
MLD 37/38	*A. africanus*	South Africa	435	D	1
MLD 1	?	South Africa	500±20	B	3
SK 1585	*A. robustus*	South Africa	530	A	1
OH 5	*A. robustus*	East Africa	530	A	1
OH 7	*H. habilis*	East Africa	687	B	2
OH 13	*H. habilis*	East Africa	650	C	2
OH 24	*H. habilis*	East Africa	590[d]	A	2-3
OH 9	*H. erectus*	East Africa	1067	A	1
OH 12	*H. erectus* (?)	East Africa	727	C	2-3
ER 406	*A. robustus*	East Africa	510±10	D	2
ER 732	*A. robustus*	East Africa	500	A	1
ER 1470	*H.* sp.?	East Africa	770[e]	A	1
HE 1	*H. erectus*	Indonesia	953[f]	A	1
HE 2	*H. erectus*	Indonesia	815[f]	A	1
HE 4	*H. erectus*	Indonesia	900[f]	C	2-3
HE 6 (1963)	*H. erectus*	Indonesia	855[f]	A	2
HE 7 (1965)	*H. erectus*	Indonesia	1059[f]	C	1-2
HE 8 (1969)	*H. erectus*	Indonesia	1004[f]	A	1

[a]A, direct water displacement of either a full or hemiendocast with minimal distortion and plasticine reconstruction; B, partial endocast determination, as described by Tobias (1967, 1971); C, extensive plasticine reconstruction, amounting to half the total endocast; D, determination based on the formula V = f ½ (LWB + LWH), described by MacKinnon et al. (1956), where L = maximum length, W = width, B = length, bregma to posterior limit of cerebellum, H = vertex to deepest part of temporal lobe and f appears to be a taxon specific coefficient.

[b]An evaluation of 1 indicates the highest reliability, 3, the lowest.

[c]Postulated for adult—the value of the actual specimen is 404 ml.

[d]Possible overestimate.

[e]Provisional estimate.

[f]These values are as yet unpublished and should be regarded as provisional.

At the present stage of our knowledge, it is premature to go beyond this kind of simple exercise. Our samples are extremely

small, we have no good empirical evidence for any early hominid body weight and the values in figure 17 connect lineages that are geographically separated (i.e., the South African gracile *Australopithecus* with the East African *Habilis* with the East Asian *Homo erectus* with modern *Homo sapiens*). Nevertheless, these relationships between brain and body weight hold great promise for better understanding the dynamics of hominid evolution. Indeed, as is clear from figure 17, one can draw the lines in different ways, with constant slopes (i.e., 1.0) or with different slopes at different times. (See also Holloway, 1974a.) The implications are extremely important, even though the basic data are admittedly weak, for the lines in figure 16 demonstrate that a number of alternative hypotheses about hominid brain evolution can exist, and that any particular hypothesis is based on assumptions of body weight that cannot be empirically pinpointed. In any event they do show a human, rather than a pongid, pattern in terms of relative brain size and changes through time, which strongly suggests that hominid brain size increase and attending selection pressures were probably unique.

TABLE 3
Some Average Brain:Body Ratios for Various Animals[a]

	Brain:body weight ratio
Homo sapiens[b]	1:45
Gorilla	1:200
Chimpanzee	1:185
Macaque, Rhesus	1:170
Marmoset	1:19
Squirrel monkey	1:12
Elephant	1:600
Whale	1:10,000
Porpoise	1:38

[a]From Cobb, 1965.
[b]Good tabulated data on ranges for healthy human adults is lacking. The exception is one study on Danes by Pakkenberg and Voigt, 1964, p. 297, in which normal brain:body weight ratios are shown to vary from approximately 1:28 to 1:80.

TABLE 4

TABLE 4
Some Possible Brain Size: Body Weight Ratio and "Progression Indices"[a]

Specimen	Average Brain Size (ml.)	Assumed Body Weight (Pounds)	Brain: Body Ratio	"Progression Index" PRG/BG
Gracile australopithecine	442	40	1:41	21.4
		50	1:62	18.7
		60	1:51	16.9
Robust australopithecine	530	50	1:43	22.3
		60	1:51	19.9
		75	1:64	16.9
		110	1:94	12.8
Homo sapiens	1361	150	1:45	28.8
Homo erectus	930	92	1:45	26.6
		125	1:61	22.0

[a]Based on Stephan's, 1972, formula using a basal insectivore line (see text).
Note: Maximum PRG/BG for gorilla is about 7.0, and for the chimpanzee, about 12.0. See Stephan, 1972, for ranges.

Maximum body weight of average gracile australopithecine (442 ml.) with PRG/BG of 12, is 100 pounds. That is, if we allow the "progression index" of *Australopithecus* to be the maximum chimpanzee value, the body weight is calculated to be 100 pounds, which is clearly too heavy, based on the postcranial materials we have thus far discovered for the gracile form of *Australopithecus*.

4. Lateralization and Cerebral Hemispheric Dominance: Comparative neuroanatomy has not been able to demonstrate any definite difference between the human brain and the ape brain except on the basis of size. Absolute and relative brain sizes, plus quantitative differences in amount of cerebral cortex in certain lobes, such as the parietal and temporal, are all that have been defined. These are matters of continuity, as far as can be established at present. The cortico-cortical fasciculus occipito-frontalis, a long associational tract known to exist in the human brain, has not been distinguished in the chimpanzee or cercopithecoid brain (Bailey et al., 1943). This does not mean that an associational system does not exist between the posterior and frontal segments of the chimpanzee cortex, but only that it is probably not so developed as it is in *Homo sapiens*. Many more pongid specimens should be dissected before its presence or absence can be proved.

TABLE 5
Brain:Body Weight Double-Log Relationships Based on the General Formula $h = bk^x$,
with Possible Slope Differences Depending on Brain and Body Weights Used[a]

Specimen	Brain Volume (ml.)	Body Weight (pounds)			Slope
Australopithecus	450	40	50	60	
					1.0
H. erectus	930	83	103	123	
					1.0
H. sapiens	1361	123	150	180	
Australopithecus	450	40	50	60	
					0.6
H. erectus	930	115	143	180	
					0.6
H. sapiens	1361	200	200	250	
Australopithecus	450	85-86	–	–	
					1.92
H. erectus	930	123	–	–	
					1.92
H. sapiens	1361	150	–	–	
A. africanus	450	50	–	–	
					1.0
H. habilis	775	86	–	–	
					0.6
H. erectus	930	114	–	–	
					1.75
H. sapiens	1361	140	–	–	

[a]Brain weights are held constant, the slopes varied and the resulting body weights determined by projection to the abscissal axis, which is the body weight.

The most singular difference known to exist at present is that the human brain is characterized by cerebral hemispheric dominance and a high degree of laterality. In general the left hemisphere seems dominant, in terms of language phenomenon, in the inferior parietal lobe (Wernicke's area), in the gyri and sulci of Heschl and in the third inferior frontal convolution, often known as Broca's area. The right hemisphere, particularly the parietal lobe, seems "dominant" for spatiotemporal and

POINTS RESULTING WHEN X = 1
POINTS RESULTING WHEN X = 1.92
POINTS RESULTING WHEN X = 0.66
COMPOSITE POINTS USING ALL THREE SLOPES
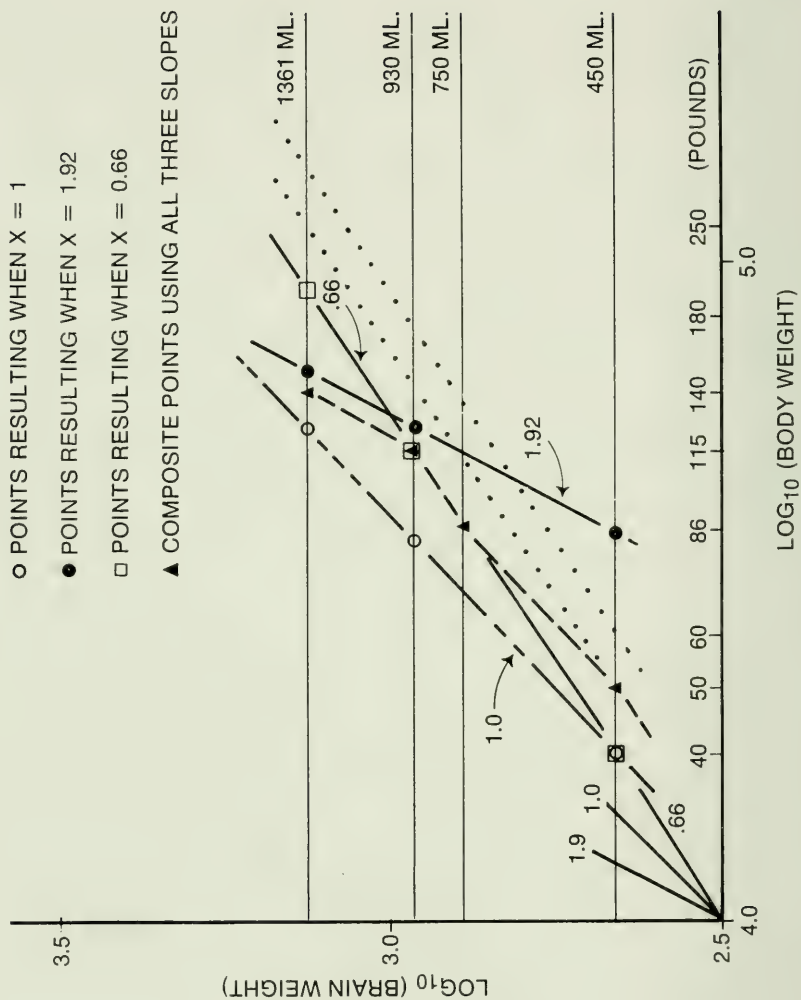
LOG₁₀ (BODY WEIGHT)

LOG₁₀ (BRAIN WEIGHT)

28

FIG. 17. Double-log (base 10) graph showing some possible regression lines, depending on assumptions of body weight, and allometric growth equation of exponential form $h = bk^x$ or $\log_{10} h = \log_{10} b + x \log_{10} k$, where h = brain weight in grams, k = body weight in grams, and x = slope of line. Average for gracile australopithecines is taken as 450 ml., *Homo erectus* as 930 ml. (based on my unpublished determinations for six endocasts) and 1361 ml. as the average for modern man, based on Tobias (1971). A slope of 0.66 is usually regarded as the best slope for all mammals (see, for example, Stephan, 1972).

This diagram shows that a number of possibilities exist and that the general slope of 0.66, if maintained throughout hominid evolution, results in body weights for modern *Homo* that are too heavy. Most slope possibilities suggest genuine selection for heavier brains. It should be realized that a number of alternative lines can be drawn. For example, the line of slope = 1.0 is based on a 40-pound body weight for the gracile australopithecine. Shifting that line over to 50 or 60 pounds gives more realistic body weights for *Homo erectus* and modern man. The composite line through the triangles has three different slopes, indicating changing selection pressures for allometric growth relationships through time. Another limitation to keep in mind is that the basal values for brain weight come from three different types of populations, the higher values coming from Asian fossils and a world-wide average for modern man. All of these slopes and figures are approximations only, taken from graph projections.

visual integration. These attributes have long been discussed in the literature, but they have never been demonstrated by gross measurements, either on the brain or on endocasts of modern *Homo sapiens*. However, Geschwind and Levitsky (1968) have shown that when the temporal and parietal lobes are cut away, the left side shows strikingly enlarged convolutions, the gyri of Heschl, underneath. Astakhova and Karacheva (1970) have shown that differences between left and right hemispheres are present before birth. It is not possible to go into all the functional details, but they can be taken as a species-specific attribute of human brain structure, and by extension, of behavior.

Do the fossil hominid endocasts show such differences? Unfortunately the endocasts of the South and East African australopithecines are seldom bilaterally complete, which precludes any direct measurements. Gross measurements, such as lengths, arcs, breadths and heights, do not demonstrate any consistent asymmetries on complete endocasts. LeMay and Culebras (1972) have suggested that the Neanderthal brain cast from La Chapelle-aux-Saints shows laterality, but this depends on how carefully the Sylvian fissure is defined in its posterior course, a feature generally impossible to observe on most endocasts.[1] LeMay and Culebras's angioradiography of living humans does, however, show consistent left-right differences, but until a more accurate and sensitive method to measure endocasts of fossil hominids is found cerebral dominance in fossils cannot be proved. I am currently working on some of the newer *Homo erectus* fossils from Indonesia, on the basis of which a case may be made for cerebral dominance, but it is too early to be certain. The presence of stone tools, of primitive, but nevertheless standard patterns, at least 2.6 to 3.0 million years old, is suggestive of both lateralization and of primitive communication by a language based on symbols (Holloway, 1969).

[1] I have not been able to see this fissure clearly on any fossil hominid endocasts I have examined.

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SUMMARY OF DIRECT AND INDIRECT EVIDENCE

In summary, we find among the early australopithecine examples fairly clear-cut evidence for human, rather than ape-like, brain organization. This is based on the following evidence:

1. The endocasts show a more human shape, particularly in the posterior migration of the lunate sulcus, which separates the primary visual cortex from the parietal association cortex, signifying an expanded associational cortical zone. The temporal lobe, so often implicated in memory mechanisms, is expanded in the anterior pole and in the inferior posterior region. The orbital rostrum is very unlike that of the apes, and there is a suggestion of an enlargement in the third inferior frontal convolution, the so-called Broca's area, which is involved in motor control of speech.

2. Indirectly, the locomotor, manipulatory, dental, and total skeletal evidence indicates a human musculoskeletal organization that presumably required neural reorganization to operate in human behavior patterns.

3. The faunal associations suggest an adaptation based on scavenging and/or hunting for animal protein. The stone tools known from this early period are made to standard patterns. Both the faunal associations and stone tools are indications of human behavior requiring reorganization at almost all levels of the brain (Holloway, 1970), from sensorimotor integration and finesse, through set and attention variables, to memory (the organization of experience and the storage, recall and reconstitution of elements).

4. Tentative brain:body ratios and encephalization indices support (but do not prove) a human brain organization.

THE STAGES OF HOMINID BRAIN EVOLUTION:
A POINT OF VIEW

So far I have discussed both direct and indirect evidence to support the suggestion that the human brain had an early beginning regardless of its absolute size. All I have said thus far applies to endocasts, and thus to the brains of the early

hominids. Brains evolve in both material and social contexts. It is my contention that human social behavior has very old roots, not only in the sense that we have evolved from some primitive apelike lineage, but in the sense that human social behavioral evolution occurred early and was the major stimulus for further evolution since the time of the australopithecines. I would like to try to put together the story of the reorganization of the hominid brain, its great increase in size and the evolution of human behavior in a synthesis that avoids some of the simplistic one-to-one linear relationships that physical anthropologists are prone to make, such as that tools made the brain evolve or that tools replaced the canines.

In this section I wish to return to the original questions: How did the human brain evolve to its present state? How can we interpret the large increase in brain size from *Australopithecus* to modern *Homo sapiens*?

It is apparent that part of this increase must be related to increase in body size. Exactly how much is difficult to say, since it depends on which animal body and brain weights we compare with man and how we regard "extra" or "vital" neurons (Jerison, 1963, 1973). Taking the average human brain weight as 1450 grams and the average body weight as 150 pounds, the following different calculations can be made: (1) Using Jerison's (1973, p. 44) equation of $E = 0.07 P 2/3$ (E = brain weight, P = body weight) for higher vertebrates, we get an expected brain weight of 108 grams for *Homo sapiens*, leaving 1342 grams as "extra" (not related to body weight); (2) If we use Stephan's (1972) equation for "basal insectivores," the expected brain weight is 475 grams, leaving 975 grams as "extra"; (3) Jerison's (1973, p. 391) equation of $E = 0.12 P 2/3$ for higher primates gives an expected brain weight of 223 grams, leaving 1227 grams as "extra."[1] Both Jerison equations

[1] I am using "extra" purely in the operational sense that it exceeds a weight based on a log-log regression with an exponent of roughly 0.6. I do not believe that any neural elements are in any other sense "extra," whether in terms of weight or numbers of neurons. The so-called extras are part and parcel of the animal's adaptive behavioral repertoire!

leave us with the same degree of encephalization as the dolphin.

Obviously these figures leave much to be desired, as the formulas are based on regressions relating only to living species. We would need to know the regressions for our fossil ancestors (*Ramapithecus*, *Australopithecus*, *Homo erectus*, etc.) to know what the increase in brain weight relative to body weight has been. If we use the mean of 442 cc. for the brain weight of the gracile australopithecines and 45 to 50 pounds as body weight, the brain:body weight ratio is about 1:45, roughly the same as modern *Homo sapiens*. If this ratio remains constant, i.e., at an exponent of 1.0, then none of the increase (*ca.* 1000 ml.) is "extra," at least in terms of the hominid regression equation.

As can be seen, the figures can be used in various ways. It is all the more curious, then, that, contrary to most opinions (Jerison, 1963, 1973), the present data on neuron numbers in the primate cerebral cortex (see, for example, Shariff, 1953) do not indicate that the increase in brain size in *Homo sapiens* is primarily a result of hyperplasia, or the addition of large numbers of neurons. From Shariff's (1953) data, modern man seems to have about 1.25 times as many neurons as a healthy chimpanzee. Jerison's (1963, 1973) calculated "extra" cortical neurons are at total variance with Shariff's data, the only empirical evidence existing for primates. According to Jerison (1963), *Homo sapiens* has 2.2 times as many cortical neurons as a chimpanzee, yet his equations for "extra" neurons are derived from Shariff's empirical histological counts (see Holloway, 1966a, 1974a, for a further critique).[1]

From limited neuropathological data, there is a suggestion that healthy chimpanzees and gorillas might have fewer mature functioning cortical neurons than human microcephalics (Holloway, 1964, 1968; Lenneberg, 1964, 1967). The behavioral repertoire of microcephalics is certainly limited, but many of

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[1]This preoccupation on mass can also be found in Count (1973), who transformed neuron numbers from base 10 to 2; i.e., humans have 2^{33} neurons, while chimpanzees have 2^{31} neurons. Count suggested that thus only two mitotic divisions separates the chimpanzee from the human brain. I strongly disagree with this interpretation.

them can use language, and their behavior is hardly simian. This further suggests some basic reorganization of the brain.

Most scientists agree that the major increase in brain size is most likely related to hypertrophy, or increase in size, of the elements. The cortical neurons are generally large in man, there is a reduction in their density and an increase in both dendritic branching of the receptive processes of the neurons and in the number of neuroglial cells supporting the neurons. Thus, one important aspect of the large increase in brain size seems attributable to the reorganization of numerous component structures. That is why I believe comparisons based on cranial capacities alone are meaningless. One cc. of chimp or australo-pithecine cortex is not equivalent to one cc. of modern human, Neanderthal or *Homo erectus* cortex. It is changes in the spatial relationships between elements that provide our great neural complexity, for these result in an enormous number of synaptic contacts, or switching points (Holloway, 1964, 1966b, 1967, 1968).

The great increase in brain size can best be related, I believe, to a matrix of interacting variables of neural and behavioral complexity during the Pliocene and Pleistocene epochs that had an essentially positive feedback structure (see Holloway, 1967). The matrix involved a change in endocrine-target tissue inter-action, an increased postnatal dependence of offspring on parents, delayed maturation and the growing role of social programming on the brain. This interpretation is based on (1) observations regarding the effects of hormonal manipulations on such brain parameters as average cortical neuron size, neuron density, dendritic branching, glial/neural ratios, and cortically-mediated behavior; (2) phylogenetic and ontogenetic changes in cortical histology; and (3) the effects of enriched and deprived environments on cortical neuron histology. I (Holloway, 1964, 1968) have reviewed this elsewhere and will not repeat the discussion here. The basic concordance in mammals between phylogenetic and ontogenetic development and extra environ-mental training on the one hand, and neurological changes—decreased neuron density, increased dendritic branching and

increased glial/neural ratios in animals treated with growth hormone or thyroxin—on the other, is illustrated in table 6. The table suggests a concordant picture of increase in brain complexity and cortically-mediated adaptive behavior. Thyroidectomy and sensory deprivation, however, produce opposite results.

TABLE 6
Concordances of Different Lines of Evidence and Various Neural Parameters[a]

Type of Evidence	Neural Parameters				
	Average Size of Neurons	Neuron Density	Glial: Neural Ratio	Amount of Dendritic Branching	Cortically-Mediated Adaptive Behavior
Ontogenetic (growth)	+	–	+	+	+
Phylogenetic (within primates, related to brain size)	+	–	+	+?	+
Physiological manipulation					
1. throidectomy	–	+	–?	–	–
2. administration of thyroxin	+	–	+	+	+
3. growth hormone	+	–	+	+	+
Environmental manipulation					
1. Sensory deprivation	–	+	–	–	–
2. Environmental complexity and training augmented (rats) (ECT vs. IC)[b]	+	–	+	+	+

[a]As the size of the neuron increases, so does its perikarya and cytoplasm, thereby requiring more neuroglial cells to service its metabolic needs. The additional size means reducing neural density, i.e., the number of neural nuclei in a standard size cube of cortical tissue. They are thus packed together less tightly. The increased neuron size also provides more cytoplasmic material for dendritic and axonal processes. Notice particularly that the hormonal evidence (all of it *in vivo*) matches the ontogenetic, phylogenetic, and environmental lines of evidence.

[b]See Holloway, 1966a, and Rosenzweig, 1972, for details.

Anthropological interpretations of the increase in brain size generally attempt to relate the increase in cranial capacity essentially to single aspects of evidence, such as tool-making,

hunting, language, etc. As the fossil hominids show an increase in endocranial volume, the archaeological record shows a concomitant increase in the range and sophistication of stone tool assemblages and in the size and kinds of animals hunted. A statistical correlation does not, of course, necessarily mean a causal connection. I find it very difficult, if not impossible, to draw a causal connection between brain size and stone tools or hunting habits. These must surely tie in more with social programming or learning than with an increase in neural elements.

It would be a great oversimplification, if not a mistake, to relate cranial capacity in any linear or causal sense to the increasing complexity of stone tools during the Pleistocene. Early hominids accomplished more than simply making stone tools for future archaeologists' digs. Their tools were used in a variety of different environments, and their cooperative social behavior was an important part of adaptation to a hunting and gathering existence. Hunting and associated activities require a complex organization involving not only perceptual and motor skills, but an understanding of animals and their habits, plants, terrain, spoor, tracks, anatomy, butchering techniques, and perhaps storage. It is the total range of cultural adaptations that relates to brain increase; the making of stone tools is only one example, and of course, the most permanently recorded one.

To the extent that the hunting of large animals involved cooperative enterprise, selection would certainly have favored behavioral mechanisms facilitating communication, including symbolic language. Language would have led to increased complexity of social interaction, involving appreciation of numerous related cues from social and material environments, and the control and inhibition of responses. In short, the increasing complexity of stone tools indicates other processes, but it cannot lead to more than educated guesses about the ecological complexity of selection pressures for human biosocial adaptations. (These relationships between tool-making and language, and hunting behavior and various levels of neural

structure have been examined in greater detail by Holloway 1964, 1969, 1970.)

Although the australopithecine brains were small, they were larger, both relatively and absolutely, than those of the chimpanzees, which probably had similar body weights. Between the chimpanzee or the gorilla and man there is a large difference in the duration of the growth period. Maturation is complete in a chimpanzee at nine to 11 years, whereas in man it takes about 20 to 25 years.

As yet we cannot look at a fossil and say at what age it became fully adult; but we must assume that growth rates and durations changed over the course of human evolution. One cannot get a brain to evolve in size without prolonging the period of its growth. Growth is a complex process involving interaction among genetic instructions for locus and timing, tissue differentiation, hormone environment (growth hormones, thyroxin, and androgens) and proper nourishment (including social nourishment). One of the organs most vulnerable to malnourishment is the growing brain, particularly during periods of mitotic division and nerve cell enlargement. The earliest evidence of increase in brain size in the fossil record coincides with the earliest evidence for utilization of protein-rich food (animal flesh). It seems an inescapable conclusion that there was an adaptive relationship between hunting and the evolution of the brain, mediated through longer periods of growth and dependence.

A SPECULATIVE MODEL OF HOMINID EVOLUTION

What follows is a set of speculations concerning the interrelations among a number of complex variables at different levels (anatomical, physiological, neuroanatomical, ecological, and social). The main purpose of this model is merely to show the matrix of variables that I believe must be considered if we are to have a clearer understanding of how the human brain evolved.

Beginning with *Ramapithecus* (10 to 14 million years ago)

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one can postulate that adaptations based on a savanna environment (utilization of seeds, grass, and other vegetation) led to strong positive selection for bipedalism. I do not think we can speculate further without additional material. Consequently, my model starts after the *Ramapithecus* level of adaptation.

Stage 1: Early australopithecine phase. Major emphasis on social behavior adaptations, involving bipedalism, endocrine organization, and brain reorganization.

Stage 2: Late australopithecine-"habiline" phase. Major emphasis on consolidation and refinement of Stage 1.

Stage 3: Late "habiline"-early *Homo erectus* to Neanderthal-*sapiens* phase. Emphasis on elaboration of cultural skills through a positive feedback relationship and brain enlargement.

Stage 1 includes the rudimentary development of cooperative, sex-role-separated social groups resulting from endocrine changes involving hormones and target-tissues. There was a reduction of sexual dimorphism in tooth and skeletal size and an increase in epigamic features of secondary sexual characteristics such as permanent breasts and fat distribution. There were possibly other changes facilitating continuous sexual receptivity of the female and closer affective relations between the sexes. This complex of correlated anatomical, physiological, and behavioral changes led to greater sexual and social control associated with prolonged periods of postnatal dependence and learning. Changes in the interactions between hormones and target-tissues could have led to a reduction in aggressive components of behavior, sexual dimorphism in size and increased periods of growth with delayed maturation of skeletal development. These processes are mediated in a complex manner by the androgens and involve other hormones as well. The endocrine changes that led to the dimorphic features cited above could have played an important role in decreasing intragroup aggression, permitting groups to live more densely. In other words, the changes led to an increase in cooperative behavior (both among males and females and among males) that meant a stronger protection against both predators and other hominid groups. At the same time they affected growth rates,

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accounting for longer periods of dependency and postnatal growth during which the brain showed an allometric increase. Associated with this complex of correlated changes are the developments of language (using a primitive symbol system) and hunting and scavenging (with a greater effective range due to more advanced bipedal locomotion).

I regard the development of language as more closely bound up with social affect and control than with hunting behavior involving signaling and "object naming," although this does not mean that hunting could not have been a strong positive selection factor for language.[1] In addition to reorganization of social behavior and bipedal adaptation, there was a reorganization of the brain involving, minimally, a decrease in primary visual cortex on the convex cerebral surface and an increase in parietal and temporal association cortex, allowing for greater discrimination among complex cues of the environment and for extension of foresight and memory to cope more effectively with the savanna-type environment. Associated with these is the early manufacture of stone tools to extend the economic base. The tools may have been used to break bones to secure marrow and to detach peices of flesh or skin. They may also have been used as missiles to drive off carnivores from their kills. The latter behavior involved not only cooperation among group members, but skill in coordinating hand-eye movements and a complex appreciation of spatial-visual calculation. It is very tempting to relate this kind of behavior with the right hemisphere, known to be dominant in such coordination.

Stage 2 includes refinement and elaboration of the changes in social behavior begun in Stage 1, as well as an increased dependence on social cohesion, language, and stone tools.

[1] I do not agree that human cognition, and more particularly spoken and gestural communication are mainly cortical-to-cortical events, "liberated," so to speak, from limbic influences. Emotional involvement and tonus is always present in human communication, except perhaps in cases of psychopathology. This does not mean that evolutionary changes in cortical tissue and hemispheric relationships were not necessary. I only mean that those changes were not merely additive, but totally integrated with noncortical structures, particularly the thalamus, limbic structures, hippocampus, and reticular formation.

Bipedal locomotion was essentially fully human. There was both relative and absolute expansion of the brain, associated mainly with increased body size. There was greater efficiency of economic sharing and cooperation between the sexes,[1] providing the basis for longer periods of postnatal dependency and learning, which initiated a feedback system between brain and cultural behavior. Language behavior became more strongly developed, and cognitive behavior of a more nearly human type developed, where language and tool-making arose from the same psychological structuring. There were true stone tool cultures at this stage, and language had prime importance in maintaining social cohesion and control and in "programming" offspring. Dependence on hunting increased and there was more success in stalking and hunting larger game. There was a selection for increased body size, bipedal agility and predictive abilities for more successful hunting. The social behavioral changes outlined in Stages 1 and 2 permitted longer male-male association for persistent hunting and for the protection of a more secure home base for females and young, who were providing small game and vegetables. The "initial kick," or "human revolution," is fully set and leads to Stage 3.

In Stage 3 a positive feedback between brain development and cultural complexity was mediated through the increased periods of dependency and learning (which was taking place in a more complex and stimulating material and social environment) of the offspring. The major neural changes are those of size and refinement of the reorganized human brain (that is, sensorimotor, associative, extrapyramidal modulation, and cerebellar involvement in manual dexterity). This is not a stage of behavioral innovation, but an elaboration of "complexity-management" involving fineness of sensory discrimination and association between larger sets of past memories and skills (see Holloway, 1967).

[1]No chauvinistic intents are harbored in the speculative model, in terms of either male or female superiority. I view the evolution of sex differences, both in behavior and morphology as complementary to human evolution, not as competitive or supraordinative.

It must be emphasized that I see these stages as gradual and continuous, with certain developments stressed more strongly in one stage than in another. My main point is to show that social behavior mechanisms have had a long development, beginning with the early hominids. In a sense, increase in brain size is minor compared to the evolution of the social matrix. Brain expansion finally depends on a solid behavioral foundation. My model takes into account both the skeletal remains and the cultural evidence and provides a base for synthesizing anatomical, behavioral (social and individual), physiological, adaptational, and ecological variables.

It is possible, I believe, to consider more molecular analyses within this model. At the level of neuroanatomy, one can suggest various brain regions that could be correlated with behavioral attributes such as set and attention, concentration, "memory" (permanence, quantity, facility, and strategy of recall), hand-eye and running coordination, mother-infant affect, babbling and reticular core reorganization, cerebral lateralization, play, curiosity, prolongation of prepubertal vividness of experience, memory, and so on. To do so, however, is far beyond the limits of this lecture.

It must be understood that the analysis of endocranial casts alone cannot play more than a limited role in elaborating my hypothesis, or in supporting my speculations. The external morphology of endocasts provides clues, not proof, about past selection pressures, and these clues are fairly gross. The judicious use of endocasts, both as clues to neural reorganization and to changes of growth variables must await further discoveries with firm dates. While studies of australopithecine endocasts are in progress, it should be apparent that the specimens have potential use, both as clues to general events in hominid evolution and as morphological patterns for taxonomic purposes. The analysis given thus far shows, I believe, that the evolution of the brain has always been an integral part of hominid evolution and was not something that took place following other changes in different morphological sectors of the hominids.

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Let me close by asserting my belief that human behavior is a long-standing evolutionary development, possibly more than three million years old. Human thought, aside from its more sophisticated scientific recency, is no late invention, but instead is very old. The human brain is both the product and cause of the evolution of human social behavior, and we should recognize that our brains are both the instruments and products of our sociality, the genesis of which was long in the making.

ACKNOWLEDGMENTS

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PERSISTENT PROBLEMS IN THE PHYSICAL CONTROL OF THE BRAIN

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FORTY-FOURTH

JAMES ARTHUR LECTURE ON

THE EVOLUTION OF THE HUMAN BRAIN

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JAMES ARTHUR LECTURES ON
THE EVOLUTION OF THE HUMAN BRAIN

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PERSISTENT PROBLEMS IN THE PHYSICAL CONTROL OF THE BRAIN[1]

INTELLECTUAL AND SOCIAL CLIMATE AND SCIENTIFIC DISCOVERY

There is great temptation to dramatize scientific discoveries by picturing them as the result of sudden insights or lucky accidents. In actuality, this is seldom the entire story since most discoveries also reflect the intellectual and social climate of their time. The many potentially significant observations that were neglected or misinterpreted attest to the importance of a prepared mind. It is true, for example, that Luigi Galvani observed a suspended frog twitch in synchrony with flashes of lightning, but this event was significant because it occurred at a time of increasing interest in the relation of physical and biological phenomena. Galvani's observation occurred only a short time after Mesmer's suggestion that "animal magnetism" was the basis of what is now called hypnotism. Not very many years earlier, the Scottish anatomist John Hunter and the English physicist Henry Cavendish speculated that the study of such electric fish as the eel and torpedo (an electric ray fish) might help to explain the action of nerves in general. In fact, the part played by electric fish in the early history of bioelectricity and electrotherapy has been the subject of an interesting essay by Kellaway (1946).

Galvani's observations, therefore, were not entirely accidental. It is certain that Galvani did not suspend a frog between a wire attached to a lightning rod and a rod immersed in a well by mere chance. He was very much aware of Benjamin Franklin's demonstration that atmospheric electricity could be

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tapped in a harmless manner. This particular frog experiment was clearly only one of many Galvani designed to study the role of electricity in biological phenomena. Many of these experiments involved the observation that a frog's muscle would twitch when touched with metal probes. The lively dispute between Galvani and the physicist Allesandro Volta that took place between 1790 and 1798 was over interpretation. Galvani argued for the existence of "animal electricity," whereas Volta argued for "metallic electricity" and claimed that the dissimilar metals used in most of Galvani's experiments produced an electric force that caused the muscles to contract. This controversy shaped much of the research on the nervous system during the early part of the nineteenth century. By 1848 when du Bois-Reymond published his book, *Investigations of Animal Electricity*, and Helmholtz had shown that the speed of nerve conduction was very different from that of electric current, the controversy had disappeared.

The value of electrical stimulation to study the nervous system, however, increased in importance with the passage of time. The technique, which had been applied primarily to the crural nerve and gastrocnemius muscle of the frog, began to be applied directly to mammal brains. Legend has it that while dressing the head wounds of soldiers, Eduard Hitzig observed that their muscles twitched on the side of the body opposite the injury. The 1870 report by Fritsch and Hitzig describing the frontal lobe regions of dogs from which electrical stimulation could evoke bodily movement is traditionally attributed to this accidental observation. As Doty pointed out, there is no truth in this legend despite the number of writers who delight in repeating it. Fritsch and Hitzig had become embroiled in the controversy over specific versus holistic representation of functions within the brain, particularly the cerebral cortex. Many investigators were using electrical stimulation to settle the issue but the results were often confusing because it was not yet appreciated that Galvanic (direct) current destroyed nerve tissue. (Du Bois-Reymond had already developed an inductorium for providing alternating or faradic current, but it was not universally used.)

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Fritsch and Hitzig concluded that their results showed clearly that "some pyschological functions and perhaps all of them . . . need certain circumspect centers of the cortex." David Ferrier reached the same conclusion a few years later as a result of his electrical stimulation of the monkey cortex. Friedrich Goltz, on the other hand, argued for holism by describing dogs that were still capable of moving all their limbs after removal of virtually half the brain. The literature of the period provides much support for the statement attributed to Alfred Binet, "Tell me what you are looking for and I'll tell you what you will find."

Even the first known attempt at psychosurgery must be examined against the background of the localization controversy. In 1891, Gottlieb Burckhardt, the director of the insane asylum at Prefargier, Switzerland, reported the results of removing part of the cortex of six "demented" patients. He said: "Who sees in psychoses only diffuse illness of the cortex . . . for him it will naturally be useless to remove small parts of the cortex in the hope to influence a psychosis beneficially by this means. One has to be as I am, of a different opinion. That is, our psychological existence is composed of single elements, which are localized in separate areas of the brain . . . . Based on these considerations and theories expressed earlier, I believe one has the right to excise such parts of the cortex, which one can consider starting points and centers of psychological malfunctions and furthermore, to interrupt connections whose existence is an important part of pathological processes."

Controversies about localization are still with us, but of course at a more sophisticated level. Stereotaxic techniques and reliable methods for permanently implanting electrodes have made it possible to undertake behavioral (psychological) studies over long periods of time. Earlier controversy was about simple motor responses; current arguments often focus on the localization of relatively complex motivational states. The intellectual and social climate also influences contemporary research, but it is difficult to achieve adequate perspective when one is very close to a scene. Nevertheless, it is helpful to try. I believe I can

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discern two major influences that have shaped brain stimulation studies from 1950 to the present. One of these involves the attempt to accumulate evidence demonstrating that electrical stimulation of discrete subcortical brain areas can evoke natural drive states. The other influence, which stems directly from the first, has been the preoccupation with brain stimulation as a technique for controlling behavior.

For psychologists interested in studying the process of learning, the early 1950s was a time of increasing disillusionment with theories based on changes in hypothetical drive states assumed to take place in the brain. (Indeed, this was a period when it was often maintained that CNS, the common abbreviation for the central nervous system, in reality meant the "conceptual nervous system.") These drive-reduction learning theories, as they are called, emphasized that we learn only (or in the weaker versions of the theory, we learn best) those stimulus-response connections that are associated with changes in level of drive state. Although it was recognized that peripheral body factors may contribute to drive state, a number of experiments had made it evident that drives such as hunger and thirst did not depend upon intensity of stomach contractions, dryness of mouth, or other obvious bodily cues. Drive states, therefore, were presumed to be represented mainly by the level of activity in functionally specific neural systems within the brain. However, this conclusion was inferential, and therefore the properties of drive, the major variable in the theory, had to be inferred and could not be measured. The field was rapidly degenerating into unresolvable arguments of little interest to anyone not indoctrinated into this specialty.

Drive-reduction theorists desperately needed some new input into their system. Although the Swiss physiologist Walter Hess had received a Nobel prize by this time, the details of his German publications were not well known in the United States. Hess had been stimulating the diencephalon in cats, using a technique that permitted him to study the responses evoked in awake, relatively unrestrained animals. Most of his observations were directed toward understanding the regulation of so-called

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autonomic responses such as changes in pupil size, blood pressure, heart rate, respiration, and the like. When Hess was invited to speak at Harvard in 1952, a number of people became aware for the first time that some of his studies seemed to demonstrate that electrical stimulation of certain areas in the diencephalon could suddenly make peaceful cats aggressive or satiated cats hungry. These reports were seized upon, for they seemed to provide a means to manipulate drives and to measure them directly.

Neal Miller (1973, pp. 54-55) reflected on his initial interest in brain stimulation studies and described it as follows:

"If I could find an area of the brain where electrical stimulation has the other properties of normal hunger, would the sudden termination of that stimulation function as a reward? If I could find such an area, perhaps recording from it would provide a way of measuring hunger which would allow me to see the effects of a small nibble of food that is large enough to serve as a reward, but not large enough to produce complete satiation. Would such a nibble produce a prompt, appreciable reduction in hunger, as demanded by the drive-reduction hypothesis?"

This certainly does not reflect the sophistication of Miller's current thinking on the problem, but it does illustrate the earlier intellectual climate that produced a need to find similarities between such behaviors as eating, drinking, and aggression when elicited by brain stimulation, and the same behaviors when motivated by natural internal states. What was found was that eating, drinking, grooming, gnawing, aggression, foot-thumping, copulation, carrying of young, and many other behaviors could be triggered by brain stimulation. What was claimed was that discrete brain centers were identified which, when stimulated electrically, would evoke specific and natural states such as hunger, thirst, sexual appetite, and maternal drives. Tests were designed to emphasize the naturalness of the evoked states and dissimilarities were disregarded or dismissed as experimental noise. A personal experience illustrates the influence of the prevailing bias. When reporting at a meeting

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that the same brain stimulus frequently evoked eating, drinking, and other behaviors, I noted that these and other observations raised some serious questions about the belief that natural drive states were evoked. A colleague attending the session told me that he had made similar observations several years earlier, but as they interfered with the planned experiments, the testing conditions were arranged so that the stimulated animals had no chance to express these "irrelevant" behaviors.

In addition to overlooking behavioral observations inconsistent with the assumption that natural drive states could be duplicated by stimulating single points in the brain, several other trends characterized the period from 1955 to 1970. There was a tendency to rush into print with every new observation of a different behavior that could be evoked by brain stimulation. The competition for priority of discovery and the need to demonstrate progress to the granting agencies often interfered with any serious attempt to understand the relation between brain stimulation and behavior change. One active researcher remarked to me that he would not be "scooped" again, bemoaning the fact that someone had published an article describing a new behavior that could be evoked by brain stimulation before he had. The list of such behaviors kept growing. One other factor that had a major impact was the belief that each evoked behavior was triggered from different and discrete brain sites. In some cases, reports encouraging the growth of this belief actually presented no anatomical information, but despite this deficiency, there was little hesitancy in using loosely defined anatomical terms (really pseudoanatomical) such as the "perifornical drinking area." Some reports presented very complete histological data, but where the authors emphasized the separateness of brain areas eliciting different behaviors, others with a different bias could just as readily see diffuse localization and considerable overlap. In total, the impression was created that a large number of natural motivational states could be reliably controlled by "tapping into" discrete brain sites.

POPULARIZATION OF RESEARCH

As the reports of these experiments began to be disseminated, a number of other distortions were introduced. These accounts fed the growing fear that this new brain technology might be used to control human behavior. The emphasis on control, by numerous demonstrations of behavior being turned "on and off" and by selective and oversimplified descriptions of these demonstrations in the popular press, has had the predictable effect. The possibility of behavior control by various brain interventions has become a popular topic for novels, television shows, movies, magazines, feature articles in newspapers, and even essays purporting to describe life in the not too distant future. Michael Crichton's *The Terminal Man* is only one of many novels that have used this theme. It may be no exaggeration to say that this story may have a greater impact (because it is believed by more people) than Mary Shelley's *Frankenstein.* Taking a different tack, an article that appeared in *Esquire* magazine described a government of the future, an "electroligarchy," where everyone is controlled by electrodes (Rorvik, 1969). It is not necessary to demonstrate that all this material is believed by everyone, or even by most people, in order to recognize that the virtual bombardment from the media has had a profound effect.

Even the material meant only for amusement, and not intended to be taken seriously, gradually begins to become a part of our serious thinking and influences our perception of interpersonal relations. A *New York Times* article dated September 12, 1971, described the scientists who: "have been learning to tinker with the brains of animals and men and to manipulate their thoughts and behaviors. Though their methods are still crude and not always predictable, there can remain little doubt that the next few years will bring a frightening array of refined techniques for making human beings act according to the will of the psychotechnologist."

With more drama and expressing less reservation, Perry London (1969, p. 37) a professional psychologist, stated that

All the ancient dreams of mastery over man and all the tales of zombies, golems, and Frankensteins involved some magic formula, or ritual, or incantation that would magically yield the key to dominion. But no one could be sure, from the old Greeks down to Mrs. Shelley, either by speculation or vivisection, whether there was any door for which to find that key . . . This has been changing gradually, as knowledge of the brain has grown and been compounded since the nineteenth century, until today a whole technology exists for physically penetrating and controlling the brain's own mechanisms of control. It is sometimes called "brain implantation," which means placing electrical or chemical stimulating devices in strategic brain tissues . . . These methods have been used experimentally on myriad aspects of animal behavior, and clinically on a growing number of people . . . The number of activities connected to specific places and processes in the brain and aroused, excited, augmented, inhibited, or suppressed at will by stimulation of the proper site is simply huge. Animals and men can be oriented toward each other with emotions ranging from stark terror or morbidity to passionate affection and sexual desire . . . Eating, drinking, sleeping, moving of bowels or limbs or organs of sensation gracefully or in spastic comedy, can all be managed on electrical demand by puppeteers whose flawless strings are pulled from miles away by the unseen call of radio and whose puppets made of flesh and blood, look "like electronic toys," so little self-direction do they seem to have.

It is little wonder that the feeling of being controlled by surreptitiously implanted brain devices has become an increasingly common delusion in paranoia.

While many people emphasize the potential misuse of these new brain-manipulating techniques, there are some who have stressed what they believe is their positive potential. They see in them a possible cure not only for intractable psychiatric disorders, but for intractable social problems as well—particularly those related to violent crimes and wars. This potential of brain intervention to achieve desirable ends has been expressed by Kenneth Clark in his presidential address to the 1971 convention of the American Psychological Association: Clark suggested that "we might be on the threshold of that type of scientific biochemical intervention which could stabilize and make dominant the moral and ethical propensities of man and subordinate, if not eliminate, his negative and primitive behavioral tendencies."

Proposals of this type can best be discussed after a more

realistic foundation is prepared for critically examining the capacity of physical techniques to modify brain-behavior relationships.

A CRITICAL EXAMINATION OF THE EVIDENCE

It should be recognized from the outset that evidence limited to the demonstration of inhibition or evocation of some behavior pattern can be very misleading. Such demonstrations convey the impression that there is a simple and predictable relationship between specific brain sites and complex behavior patterns. Also, the implication that only one behavior is influenced by the electrical stimulation encourages the inference that the control is very precise and selective.

It might not be inappropriate to begin the critical examination with a demonstration that is familiar to most people, Delgado's (1969) purported demonstration of brain stimulation inhibiting aggressiveness in a bull. An article in the *New York Times* (September 12, 1971) described the event as it is typically reported: "Dr. Delgado implanted a radio-controlled electrode deep within the brain of a *brave* bull, a variety bred to respond with a raging charge when it sees any human being. But when Dr. Delgado pressed a button on a transmitter, sending a signal to a battery-powered receiver attached to the bull's horns, an impulse went into the bull's brain and the animal would cease his charge. After several stimulations, the bull's naturally aggressive behavior disappeared. It was as placid as Ferdinand."

Although this interpretation is commonly accepted, there is actually little evidence supporting the conclusion that the stimulation had a specific effect on the bull's aggressive tendencies. A viewing of the film record of this demonstration should make it apparent to all but the most uncritical observer that the stimulation forced the bull to turn in circles in a very stereotyped fashion. This should not surprise anyone familiar with the brain, as the stimulating electrode was situated in the caudate nucleus, a structure known to play an important role in regulating bodily movements. It is true that the bull's aggressive

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charges were stopped for a short period, but there is no evidence that it was because aggression was inhibited. Rather, because it was forced to turn in circles every time it came close to its target, the confused bull eventually stopped charging. Patients receiving caudate nucleus stimulation also display various types of stereotyped motor responses. Sometimes all movement is stopped in an "arrest response," so that a person instructed to continue tapping a table may be immobilized by the stimulation with his hand in midair (Van Buren, 1966). Destruction of the caudate nucleus in cats and other animals has been reported to produce a syndrome called *obstinate progression*, a curious phenomenon characterized by persistent walking movements even when an animal's head may be wedged into a corner (Mettler and Mettler, 1942). In humans, movement disorders such as the spasticity and tremors seen in Parkinson's disease have frequently been linked to caudate nucleus pathology.[1]

Caudate stimulation has also been reported to cause confusion and to interfere with speech (Van Buren, 1963). There are several animal studies indicating that caudate stimulation interferes with the normal habituation of responses to novel stimuli when they are presented repeatedly, e.g., Deadwyler and Wyers (1972), and Luria (1973) have suggested that in humans the caudate nucleus is important for focusing attention because of its role in selectively inhibiting responses to irrelevant stimuli. Kirkby and Kimble (1968) reported that rats have difficulty inhibiting responses in passive avoidance tests following damage to the caudate nucleus, and Rosvold, Mishkin, and Szwarcbart (1958) have concluded that this structure is

[1] Plotnik and Delgado (1970) have presented evidence that stimulation of the caudate nucleus, putamen, gyrus pyriformis, and gyrus rectus may inhibit the threatening grimaces in monkeys that normally followed tail shock. Although only a minimum amount of data were presented, these changes in the monkeys' behavior did not seem to be accompanied by motor disturbances or general disorientation. Although the report suggests that stimulation of some structures may inhibit the expression of aggressive displays at current intensities that do not produce gross motor disturbances, there is no reason to assume that the large number of other functions believed to be regulated by these brain areas were unaffected.

involved in delayed alternation and visual discrimination performance of monkeys.

Many more functions of the caudate nucleus are described in the scientific literature, but a cataloguing of them all is not necessary for our present purpose. It should be clear, however, that we will not advance very far in our attempt to analyze the contribution of the caudate nucleus to behavior if we restrict ourselves to listing the complex behaviors affected by electrical stimulation. What is needed is a testing program designed to characterize functional changes with increasing precision by dissecting out the elements common to behaviors appearing to be very different.

The fact that it is possible to inhibit or evoke different complex behaviors by electrical stimulation has led some people to conclude that specific behaviors might be modified by destroying the neural area around the tip of the stimulating electrode. Thus, using the electrode implanted in the bull's caudate nucleus to destroy a portion of this structure would be expected to alter the aggressive temperament of that animal. Although the specific experiment has not been done, there is no reason to believe that this would be the case. Destruction of the caudate nucleus does not change the aggressive tendencies of other animals, but it may produce various movement deficits or impairments on tasks requiring a selective inhibition of sensory and motor processes and the connections between them.[1] Similarly, if one destroys the hypothalamic area that evokes aggressive behavior in a cat or rat, under an electrode, no change in natural aggressivity is induced unless the area destroyed is so extensive that the animal is incapable of any behavior at all. Even after surgical isolation of the entire hypothalamus, a cat is still able to display integrated attack and rage responses when

[1] None of this evidence is meant to argue against the possibility that parts of the caudate nucleus may be more involved in one type of process than in another. It has been shown that specific parts of the caudate nucleus receive input from the orbital frontal, the dorsolateral frontal, or the inferotemporal cortex, and the deficits that follow selective destruction of portions of this complex structure differ accordingly (Divac, Rosvold, and Szwarcbart, 1967). The behavioral manifestations of these deficits, however, vary with the demands of the situation.

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provoked, as Ellison and Flynn (1968) have demonstrated. Earlier, Hess described his disappointment at not being able to modify a behavior elicited by stimulation even after destroying the tissue around the electrode. He said:

"This step, involving the use of the same electrodes, seemed to be most promising, inasmuch as we expected that a comparison of stimulation and destruction effects would provide us with a reciprocal confirmation in the sense of a plus or minus effect. In reality, however, the results were disappointing. Today we know why. Since our procedure aimed for the greatest possible precision, we often produced only corresponding small foci of coagulation. As is shown by the stimulation study, however, even the best demarcated 'foci' are relatively diffuse" (Hess, 1957, p. 43).

Luria (1973, pp. 33-34) commented that localization of complex functions in specific regions of the brain is always misleading. What is needed, he said is to "ascertain by careful analysis which groups of concertedly working zones of the brain are responsible for the performance of complex mental activity; what contribution is made by each of these zones to the complex functional system."

Luria also noted that though it is appropriate to speak of the secretion of bile as a function of the liver, insulin secretion as a function of certain cells in the pancreas, and the transduction of light by photosensitive elements in the retina, when we speak of such functions as digestion or perception, "it is abundantly clear that [they] cannot be understood as a function of a particular tissue." Similarly, Luria (1973) quoted Pavlov on the question of a "respiratory center." "Whereas at the beginning we thought that this was something the size of a pinhead in the medulla . . . now it has proved to be extremely elusive, climbing up into the brain and down into the spinal cord, and at present nobody can draw its boundaries at all accurately."

The idea that the brain is organized into discrete compartments whose function corresponds to our social needs is simply not in accord with reality. The brain does not work that way. A concept such as aggression is a man-made abstraction and it

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therefore should not be expected to exist as a separate entity in the nervous system. Many parts of the nervous system play roles in regulating what most of us would label aggressive behavior and each of these parts also plays a role in regulating other aggression, and copulation. Even though all of these behaviors point. These investigators destroyed a small amount of the hypothalamic tissue in a rat by means of a specially designed knife and reported changes in eating, drinking, irritability, aggression, and copulation. Even though all of these behaviors were not affected equally, the possibility of modifying a large number of behaviors by destroying even a small amount of brain tissue is quite clear. In drawing conclusions from brain stimulation experiments, what is almost invariably overlooked is that just about *every area of the brain is involved in many different functions and all but the simplest functions have multiple representation in the brain.*

The eagerness to believe that discrete and natural motivational states such as hunger can be manipulated by brain stimulation has resulted in a selective perception of even some of the pioneering work in this field. For example, although Hess is consistently mentioned as having produced bulimia by hypothalamic stimulation, it sometimes seems that his classic papers are not read so often as they are cited. Hess (1957, p. 25) actually said the following: "Stimulation here produces bulimia. If the animal has previously taken neither milk nor meat, it now devours or drinks greedily. As a matter of fact, *that animal may even take into its mouth or gnaw on objects that are unsuitable as food, such as forceps, keys, or sticks.*" (Italics mine.)

It must be recognized that most hungry cats are more discriminating than Hess's brain-stimulated animals.

In the studies from my own laboratory, it has been shown that the behavior evoked by brain stimulation is very different from behavior motivated by natural states. A stimulated animal may eat one type of food, but not the food it normally eats in its home cage (fig. 1), or it may not eat even the same food if it is changed in texture, as when food pellets are offered as a

ground mash. Stimulated animals may drink water from a drinking tube, but not from an open dish (fig. 2), and the taste preferences of an animal drinking in response to stimulation differ from those of a thirsty animal (fig. 3). Most important from the point of view of behavior control (or lack of it), the elicited behavior may change even in response to identical brain stimulation. A rat that drinks only in response to stimulation, for example, may start to eat when stimulated at a later time (figs. 4, 5). Moreover, the brain sites from which eating and drinking may be evoked are much more widespread than is usually implied. There is no anatomically discrete focus for this phenomenon, although there are brain areas where the proba- bility of evoking eating and drinking is very low (Cox and Valenstein, 1969). In 1973 Reis, Doba, and Nathan reached a similar conclusion. These investigators found that they could evoke grooming, eating, and predatory behavior (depending on the intensity of the stimulating current) from almost all electrodes placed in the fastigial nucleus of the cat's cerebellum. Since the behaviors invariably appeared in the same order as the stimulus intensity was increased, regardless of the electrode placement within the fastigial nucleus, the investigators con- cluded (*op. cit.,* p. 847): "Thus, it is the intensity of the stimulus and not the location of the electrode which is one of the determinants of the identity of the behavior. Second, the observation that the nature of the behavior evoked from a single electrode at a fixed stimulus intensity could be changed by altering the availability of goal objects (such as food or prey) is another demonstration that the locus of the electrode is not critical. Thus, our findings suggest that the behavioral responses from fastigial stimulation are probably not due to excitation of discretely organized neural pathways."

The conclusion to be drawn from these experiments is certainly not that stimulation at any brain sites can evoke any behavior if the contingencies are arranged appropriately or that stimulation at different sites all evoke the same general state. These misinterpretations continue to appear in print although we have made an effort to be clear on these points. Valenstein,
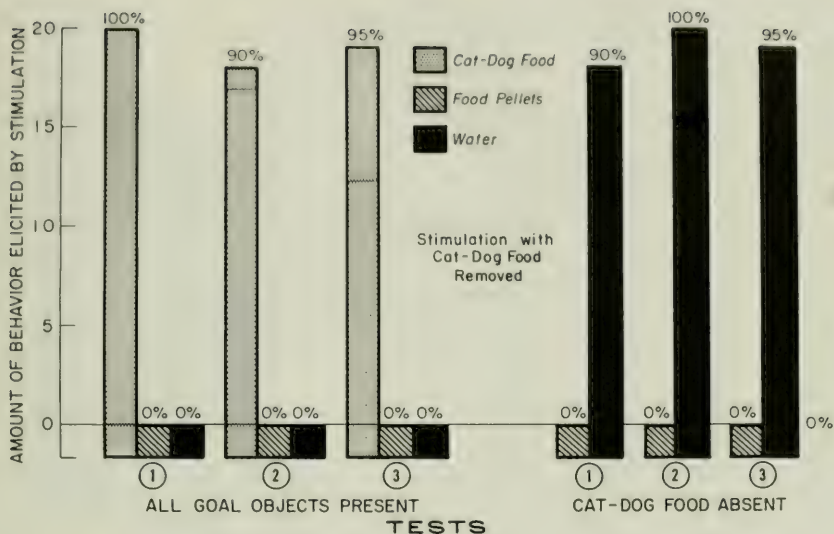
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FIG. 1. Behavior evoked by brain stimulation in a testing situation involving choices. During initial 3 tests, rats received brain stimulation in the presence of commercial cat-dog food, their regular food pellets, and a water bottle. Stimulation evoked eating cat-dog food only. Then cat-dog food was removed. We assumed that if stimulation evoked a hunger state animals would readily switch to eating food pellets. Instead, stimulation gradually evoked drinking with increasing regularity (see fig. 5). After stimulation evoked regular drinking three additional tests with food pellets and a water bottle were administered. Animals drank almost every time stimulation was given. Stimulus parameters were invariably the same. Each test consisted of 20 stimulations (20 sec. duration). Maximum score for any one behavior was 20, but animals could display more than one behavior during a single 20-second stimulation period. (Data from Valenstein, Cox, and Kakolewski, 1968b.)

Cox, and Kakolewski (1970, p. 30) said: "We are not suggesting that any elicited response may substitute for any other, but rather that the states induced by hypothalamic stimulation are not sufficiently specified to exclude the possibility of response substitution." And Valenstein (1969, p. 300) said, "[it] is not meant to imply that it will not be possible to differentiate the effects of stimulation at different hypothalamic regions, but rather that the application of specific terms such as hunger, thirst and sex may not be justified."

It seems clear that some behaviors are more likely to be

AMOUNT OF BEHAVIOR ELICITED BY STIMULATION

20

100%   100%   95%
90%   90%   85%

Water in Bottle

Water in Dish

Food Pellets

15

Drinking Experience
from Water Dish

10

Stimulation with
Water Dish and
Food Pellets

5

0   0%   0%   0%   0%   0%   0%   0%

①   ②   ③   ①   ②   ③

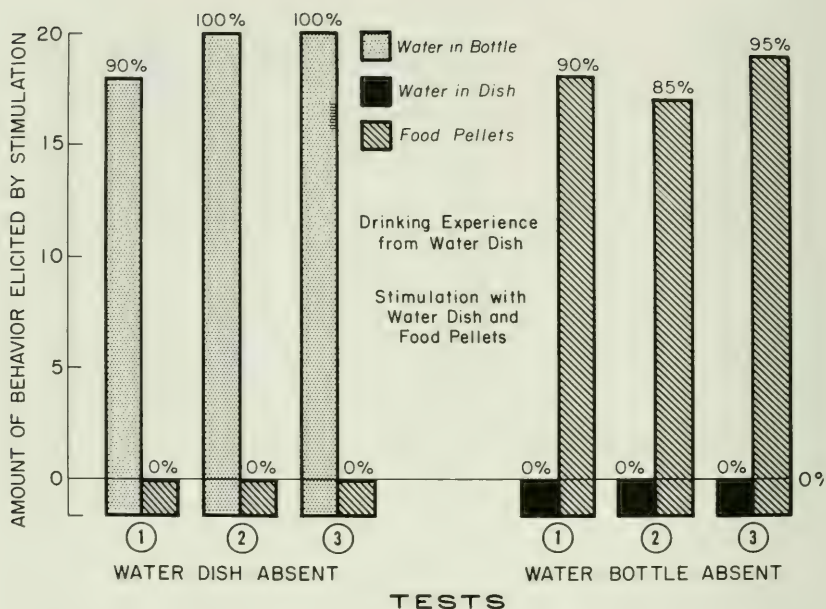WATER DISH ABSENT   WATER BOTTLE ABSENT

TESTS

FIG. 2. Behavior evoked by brain stimulation in a testing situation. During initial tests, rat drank from water almost every time stimulation was administered, but did not drink water from a dish or eat food pellets. Afterward, the animal drank all the water from a dish for three days (this was natural drinking; no brain stimulation was administered) before periodic stimulation in the presence of the water dish and food pellets were initiated. It was assumed that if thirst had been induced by stimulation during initial tests, rat would rapidly switch to drinking water from dish when stimulated. Instead, stimulation gradually evoked eating of food pellets. During three stimulation tests with water dish and food pellets available, rat did not drink, but ate food pellets during most of stimulation trials. Stimulus parameters were invariably the same. Each test consisted of 20 stimulations (20-sec. duration). Maximum score for any one behavior was 20, but animals could display more than one behavior during a single 20-second stimulation period. (Data from Valenstein, Kakolewski, and Cox, 1968.)

interchangeable than others. This probably reflects the role of the sensory, motor, and visceral changes induced by the stimulation in channeling behavior in certain directions. Although these bodily changes do not duplicate natural motivational states, they do play an important role in determining the types of behavior that will or will not be seen during stimulation.
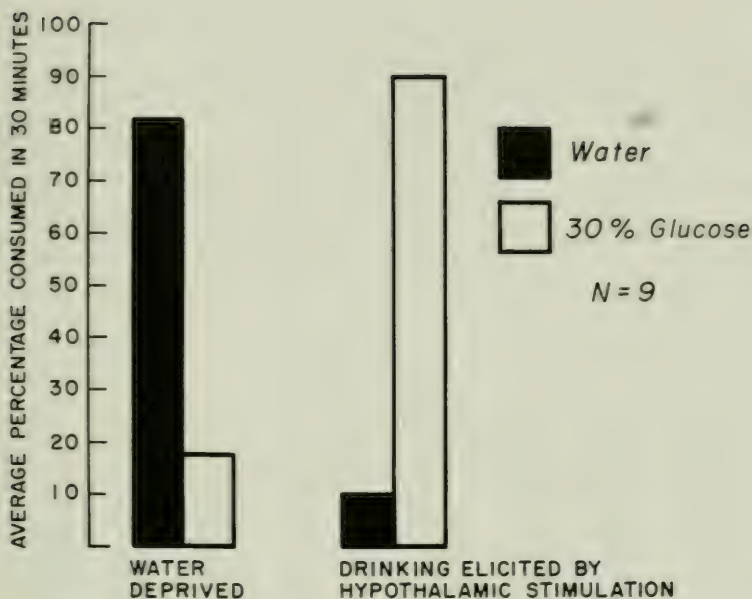
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FIG. 3. Preference for water and glucose by rats receiving brain stimulation and the same animals being deprived of water for 48 hours. All rats initially drank water when stimulated but did not eat. In a two-bottle choice test, they preferred glucose during brain stimulation, but water when thirsty. (Data from Valenstein, Kakolewski, and Cox, 1968.)

To date, the direct effects of stimulation have been relatively neglected. Although it is often stated that stimulation does not produce behavior changes unless the appropriate stimulus is available, such changes are actually often neglected even when the data suggest their importance. For example, the first description of drinking evoked by brain stimulation contained a strong suggestion that motor responses may have been more important in directing behavior than any presumed thirst state. In his report, Greer (1955, pp. 60-61) said:

Stimulation of the animal began 24 hours after the electrodes were implanted. It was immediately apparent that the animal was under great compulsion to perform violent "licking" activity when a current was passed between the hypothalamic electrodes. In response to stimulation, it would stand on its hind legs and run vigorously around the glass enclosed circular cage, licking wildly at the glass wall. This behavior

would cease immediately upon shutting off the current. If the voltage were slowly increased, licking would gradually become more vigorous. With stimulation continuing by timer control, the reaction of the animal changed during the first night. The water bottle containing 200 ml was found completely empty at 9 a.m. even though it had been filled at 6 p.m. the previous evening. It was now found that stimulation would result in violent drinking activity. The non-specific licking response had been lost. As soon as the current was turned on, the animal would jump for the water bottle and continue to drink avidly until the switch was turned off. If the water bottle was removed and the current then turned on, the rat would go back to its "licking" behavior of the previous day, but would immediately transfer it to drinking behavior when the water bottle was replaced.
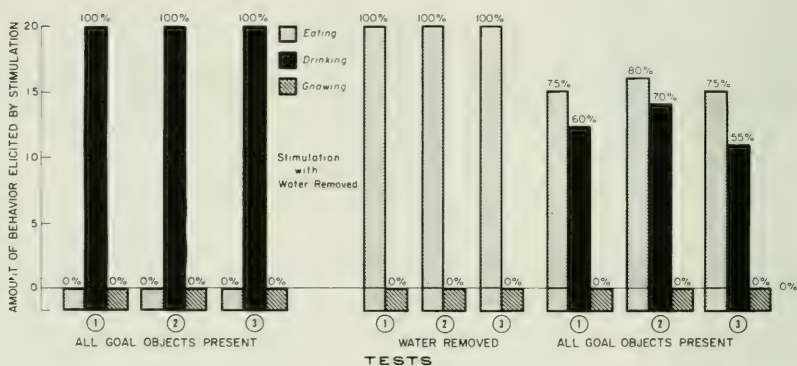

FIG. 4. Behavior evoked by brain stimulation in a choice situation. Initially, animal drank only when stimulation was given (first 3 tests). After periodical stimulation in the presence of food and a wooden block (for gnawing), but without water bottle, rat gradually began to eat food pellets. Next three tests demonstrated that stimulation evoked regular eating. Last 3 tests demonstrated that even when tested with water bottle present, stimulation elicited eating as well as drinking. Stimulus parameters were invariably the same. Each test consisted of 20 stimulations (20-sec. duration). Maximum score for any one behavior was 20, but animals could display more than one behavior during a single 20-second stimulation period. (Data from Valenstein, Kakolewski, and Cox, 1968a).

Visceral changes produced by the stimulation may also play a role in determining the behavior evoked by brain stimulation. For example, Folkow and Rubinstein (1965) contrasted the visceral changes produced by hypothalamic stimulation that evokes eating with those changes produced by electrodes evoking rage reactions. Among the prominent bodily changes
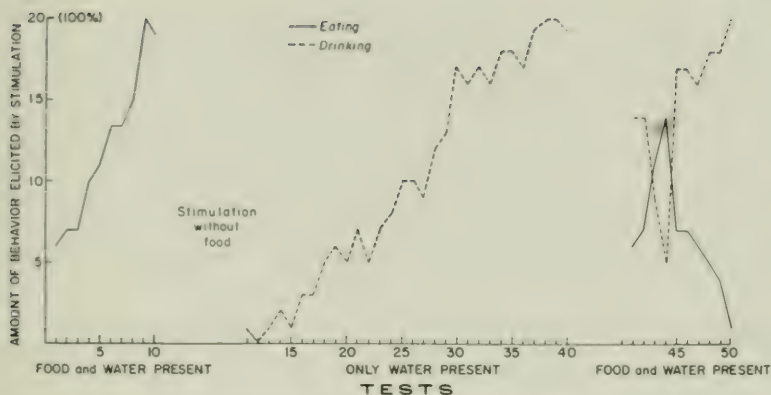
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FIG. 5. Gradual development of behavior evoked by brain stimulation. Rat was tested shortly after first demonstration of eating in response to stimulation. In more than 10 successive tests, eating was evoked by brain stimulation with increasing regularity. Although water was available, stimulation never evoked drinking. Animal was then given periodic stimulation for one-week period until it started to drink in response to stimulation. In more than 40 tests, rat drank in response to stimulation with increasing regularity. During last 10 tests, both food and water were present. During most tests rat ate and drank when stimulation was administered, although drinking gradually became dominant evoked response. Stimulus parameters were invariably the same. Each test consisted of 20 stimulations (20-sec. duration). Maximum score for any one behavior was 20, but animals could display more than one behavior during a single 20-second stimulation period. (Data from Valenstein, 1971.)

produced by stimulation that caused rats to eat were a marked increase of intestinal motility and change in stomach volume plus mild increases in blood pressure and heart rate. The pattern was different when rage was evoked; intestinal and gastric motility were inhibited, and the blood pressure and blood distribution patterns differed from those produced by electrodes that evoked eating.

Ball (1974) also stressed the importance of visceral changes for evoked eating. In rats displaying this response, Ball sectioned the vagus nerve at a point close to where it innervates the stomach. He reported that the stimulus threshold for elicitation of eating was raised significantly even after the animals recovered from surgery and were eating the normal amount of food in their home cage. Even though the thresholds increased, it was clear that the visceral changes controlled by

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this branch of the vagus nerve were not necessary for the evoked behavior, as stimulation continued to evoke eating. Similarly, as noted earlier, Reis, Doba, and Nathan (1973) reported that electrical stimulation of the rostral fastigial nucleus of the cat's cerebellum elicited either grooming, feeding, or killing of a rat, depending on the intensity of stimulation used. The magnitude of the cardiovascular responses (heart rate and blood pressure) differed for each of the three behaviors evoked, but the behaviors were still displayed after these visceral responses were blocked by an injection of phentolamine. It is evident from the many important studies by Flynn and his colleagues (see Flynn, Edwards, and Bandler, 1971) that brain stimulation produces many different sensory, motor, and visceral changes. Apparently the blocking of one or two of these changes is not likely to be very disruptive once an elicited behavior has become established. These bodily changes, however, may play an important role in channeling behavior during the initial brain stimulation experience.

In addition to producing bodily changes, the positive or aversive motivational effects evoked by brain stimulation may also serve to channel behavior and determine which behaviors are interchangeable. Plotnik (1974) summarized the motivational consequences of 174 brain stimulation sites in monkeys. The motivational effects were determined by tests that measured whether an animal sought out escaped from or was indifferent to the brain stimulation. It was found that 117 sites were neutral, 22 were positive or rewarding, and 35 were aversive or negative. All 14 points that elicited aggressive behavior directed at other monkeys had aversive motivational properties, although the converse was not true. Plotnik views the elicited aggression as "secondary aggression" produced by reaction to an aversive stimulus. In such cases, it would be as misleading to conclude that there was a direct relationship between natural aggression and the brain site stimulated as there would be to conclude the same about the soles of the feet because an electric shock delivered to them produces fighting between animals caged together. The point is well illustrated by

Black and Vanderwolf (1969, p. 448), who reported that a foot-thumping response could be evoked in the rabbit by stimulation of diverse brain sites (in the hypothalamus, thalamus, central gray, septum, reticular formation and fornix-fimbria). Rather than postulate the existence of a complex "thumping circuit" in the rabbit brain, they noted that thumping could be elicited by foot shock and concluded that "thumping behavior in the rabbit is a fear or pain response."

The significance of the motivational properties of brain stimulation is made clearer by distinguishing predatory from aggressive behaviors. In cats and rats, hypothalamic stimulation has evoked both types of behaviors. In these animals, a predatory, stalking behavior (called "quiet biting attack" in the rat), which is well directed at an appropriate prey, has been distinguished from a diffusely directed "affective rage attack" (Wasman and Flynn, 1962; Panksepp, 1971). Stimulation at sites that evoke the predatory (or appetitive) behavior has been shown to also evoke positive or rewarding effects (Panksepp, 1971), whereas stimulation at sites evoking "affective attack" has been demonstrated to be aversive (Adams and Flynn, 1966). In primates, the elicited aggression is intraspecific, resembling fighting rather than predatory behavior, and is evoked primarily, if not exclusively, by stimulation having aversive motivational properties.[1] Although the evidence is inadequate, aggression provoked by brain stimulation in humans also seems to occur only in cases of stimulation having aversive consequences (see Valenstein, 1973, for a review of this literature). Considerations such as these, suggesting that certain behaviors are compatible with aversive and others with positive states, may set limits on the behaviors that can be evoked by a particular brain electrode.

Although the somatic and motivational effects produced by

[1] Robinson, Alexander, and Browne (1969) reported one instance where stimulation elicited aggressive attacks on another monkey and also supported self-stimulation behavior. This suggests that brain stimulation that elicits intraspecies aggression may be motivationally positive. However, as self-stimulation was tested with brief (0.5 sec.) stimulus trains and aggression was elicited by relatively long (10-40 sec.) stimulus trains, this exception may be more apparent than real.

brain stimulation make it more likely that one group of behaviors will be evoked rather than another, these factors are by no means sufficient to determine completely the specific behavior displayed or the motivational states induced. Environmental factors and individual or species characteristics can also be very important determinants. An experiment from my own laboratory demonstrates this point and also illustrates how easily one can be misled by first impressions in brain stimulation experiments.

Figure 6 illustrates a two-compartment chamber used to test the behavior of rats receiving rewarding hypothalamic stimulation (Phillips et al., 1969). The equipment was so arranged that when the rat interrupted the photo cells on the right side of the chamber, brain stimulation is turned on and remained on until the animal interrupted the photo cell in the left compartment. In an amazingly short time, the rat learned to play the game, running to the right side and turning the stimulation on for a period, then running to the opposite side and turning the stimulation off. This behavior was repeated rapidly over and over again. The rat was stimulating its own brain and apparently enjoying it—at least it continued doing it.

At this point, we placed food pellets on the right, the stimulation side. After a brief period, the rat started to pick up the pellets when stimulated and carry them (as pictured in fig. 6) to the opposite side of the chamber, where they were dropped as soon as the brain stimulation was turned off. We were fascinated by this unexpected turn of events, as it seemed possible that we had stumbled on a region of the rat's brain that regulated food-hoarding behavior. At least that is what we were thinking until we investigated a little further. When we substituted rubber erasers and pieces of dowel sticks, the rat carried them just as readily. If we mixed the edible and inedible objects together, the rat did not discriminate between them. It carried both. This was a very strange type of food-hoarding behavior! Next we placed some rat pups on the right side and found that these also were carried to the other side. It dawned on us that had we started with the rat pups and gone no farther,

we would have been convinced that we were activating the brain structures that controlled the pup-retrieval component of maternal behavior. Probably we would have found it difficult to resist speculating about the significance of the fact that males carried pups as readily as females.
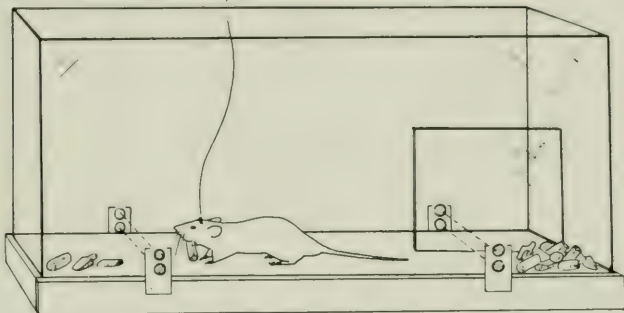

FIG. 6. Rat carrying wooden dowel stock from stimulation (right) to nonstimulation (left) side of test chamber. (In this variation of the basic experiment, animals were given a choice between receiving hypothalamic stimulation with or without the opportunity to carry objects; they chose the former.) (Data from Phillips et al., 1969; figure reproduced from Valenstein, Cox, and Kakolewski, 1970.)

Once the rats started carrying objects regularly, they would pick up and carry almost anything in response to the stimulation. When stimulated, the compulsion to carry became so strong that the rats carried parts of their own bodies when all the objects were removed. A rat picked up its tail or a front leg with its mouth and carried it over to the other side where it was "deposited" as soon as the stimulation was turned off.

Finally, we found that if the very same stimulation was delivered to the rat's brain under different conditions, objects were no longer carried. We programmed the equipment to deliver the same temporal pattern of stimulation the rat had previously self-administered, controlled now by a clock rather than by the rat's position. This procedural change resulted in the possibility that the animal could be stimulated any place in the test chamber rather than the stimulation being turned on

and off consistently in different parts of the chamber. Under these conditions the identical electric stimulus, delivered to the same brain site through the same electrode, no longer evoked object-carrying even if the animal was directly over several of the objects when the stimulation was turned on.

We believe that the answer to this puzzling phenomenon lies partly in the rat's tendency to carry objects (food, pups, even shiny objects) from an open field, where the rat is vulnerable and therefore highly aroused, back to the relatively secure and calming environment of the nest site. When stimulation is delivered regularly in certain parts of the rat's life space and turned off regularly in other parts, it not only produces alternating arousal and calming states, but links these states to specific parts of the environment. In addition, because rats prefer to turn off even rewarding brain stimuli after a period of time (Valenstein and Valenstein, 1964), they are forced to move back and forth in the test chamber. Taken all together, we may have inadvertently duplicated all the internal and external conditions that exist when a rat makes repeated forays from its nest site to the outside world.

Admittedly, this explanation is speculative. It is clear, however, that the behavior produced by stimulation is not determined in any simple fashion by the location of the electrode in the brain. (Actually, we achieved the same results with electrodes in different rewarding sites.) The behavior produced by the stimulation can only be understood by considering the natural propensities of the rat in the environmental conditions in which it is tested.

BRAIN STIMULATION IN HUMANS AND OTHER PRIMATES

If the response to brain stimulation is variable in inbred rats, it is certainly much more variable in monkeys and humans. In monkeys, for example, brain stimulation may initiate drinking when the animal is confined to a restraining chair. However, when the stimulation is administered when the monkeys are in a cage and not restrained, they do not drink, even though they

may be sitting within inches of the water dispenser when the stimulation is administered (Bowden, Galkin, and Rosvold, In press). In humans, brain stimulation may evoke general emotional states that are somewhat predictable in the sense that certain areas tend to produce unpleasant feelings and other areas tend to produce positive emotional states. Patients may report feeling tension, agitation, anxiety, fear, or anger, or they may describe their feelings as being very pleasant or relaxed. Different patients report different feelings from stimulation of what is presumed to be the same brain area, and the same person may have very different experiences from identical stimulation administered at different times (see Valenstein, 1973, for a review of this literature). The impression that brain stimulation can evoke the identical emotional state repeatedly in humans is simply a myth, perhaps perpetuated in part because of its dramatic impact. Janice Stevens et al. (1969, p. 164) stressed this variability: "Subjective changes were elicitable in similar but not identical form repeatedly on the same day, *but often were altered when stimulation was carried out at the same point on different days.*"

Many people have the impression that the results of brain stimulation are predictable because of the reports that the same visual hallucinations and memories can be evoked repeatedly by brain stimulation. It is true that Wilder Penfield, who operated on the temporal lobes of patients suffering from intractable epilepsy, had emphasized that electrical stimulation of this brain region may repeatedly evoke the same memory. Considerable excitement was generated by reports that these evoked memories had the fidelity of tape recording playbacks of past, forgotten experiences. Indeed, on the basis of these reports, a few psychoanalysts began to speculate about the neural basis of repressed memories (Kubie, 1953). What was generally overlooked, however, was that Penfield had reported that the same response could be evoked within a minute or two, but a different response was obtained after a longer period (see Penfield and Perot, 1963). The similarity of this conclusion to that of Stevens et al. (1969) is apparent. Moreover, recent

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studies have made it clear that the occurrence of these evoked memories is rare and when they do occur it can usually be shown that they were determined by what was on the patient's mind or some other aspect of the situation when stimulation was administered (Van Buren, 1961; Mahl et al., 1964).

Even relatively simple motor and sensory responses to stimulation of specific areas of the cerebral cortex of primates may vary with time and individuals. When Leyton and Sherrington (1917) reported their observations following cortical stimulation of the chimpanzee, orang-utan, and gorilla, they noted considerable evidence of "functional instability of cortical motor points." Not only did thresholds vary and stimulation of a particular brain site produce either extension or at other times flexion of the same joint, but the muscles involved sometimes also changed. Leyton and Sherrington reported that often a particular response became dominant and was elicited from a variety of cortical points that had previously given very different responses. They also observed that stimulation of the same cortical points produced different responses from different individuals and even from opposite hemispheres within the same individual. This is not to deny that there was general agreement as to the parts of the frontal cortex most likely to produce movement of some kind in specific muscle groups, but Leyton and Sherrington emphasized that the details of the movements would not be the same if the experiment were repeated. Observations of this type have also been made following stimulation of the human cortex. Penfield and Boldrey (1937, p. 402) noted that stimulation at a point on the post-central gyrus, which does not elicit a particular response, may gain this capability if it is tested after stimulating a brain point that does evoke the response. Similar observations of variation of responses have been reported following electrical stimulation of sensory cortical areas in humans. Penfield and Welch (1949), for example, noted that if a brain site evoked sensations seeming to originate in the thumb, the same stimulation might later evoke sensations experienced as coming from the lips if the stimulation had been preceded by activation

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of another site that evoked lip sensations. These authors have called such variability "deviation of sensory response." Libet (1973) discussed the variability in human response to electrical stimulation in more detail.

It is totally unrealistic to believe that stimulation of a discrete point in the brain will invariably elicit the same memory, emotional state, or behavior. The changes produced by the stimulation depend upon what is going on in the rest of the brain and in the environment at the time. The understandable need in science to eliminate variability and demonstrate control over phenomena may, when applied to the study of the brain, distort reality by concealing the very plasticity that is an essential aspect of adaptive behavior.

CONTROL OF HUMAN BEHAVIOR: FACT AND FANTASY

No discussion of electrical brain stimulation and behavior control would be complete without considering the existence of rewarding brain stimulation. As everyone surely knows by now, Olds and Milner (1954) accidentally discovered about 20 years ago that electrical stimulation of certain brain structures can serve as an effective reward for rats. Subsequent studies of the behavior of rats and other animals indicated, in many different ways, that pleasurable sensations can be evoked by brain stimulation (see Olds, 1973). No other single discovery in the brain-behavior field has produced more theoretical speculation than the phenomenon that animals are highly motivated to stimulate their own brains. Clarke's reaction (1964, pp. 200-201) to this discovery is representative:

Perhaps the most sensational results of this experimentation, which may be fraught with more social consequences than the early work of the nuclear physicists, is the discovery of the so-called pleasure or rewarding centers in the brain. Animals with electrodes implanted in these areas quickly learn to operate the switch controlling the immensely enjoyable electrical stimulus, and develop such an addiction that nothing else interests them. Monkeys have been known to press the reward button three times a second for eighteen hours on end, completely undistracted either by food or sex. There are also pain and

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punishment areas of the brain; an animal will work with equal singlemindedness to switch off any current fed into these.

The possibilities here, for good and evil, are so obvious that there is no point in exaggerating or discounting them. Electronic possession of human robots controlled from a central broadcasting station is something that even George Orwell never thought of, but it may be technically possible long before 1984.

In part, because the pleasurable reactions have been produced by direct stimulation of the brain and involve electronic gadgetry, there is a tendency to conjure up images of "pure pleasure" that are completely irresistible. It should surprise no one that science fiction writers have seized this phenomenon as a theme for their stories. In Larry Niven's story (1970), for example, the presumed omnipotence of rewarding brain stimulation is at the very center of the "perfect crime." The story takes place in the year 2123 and Owen Jennison's body has just been discovered under conditions that appear to indicate a suicide, but the death actually was the result of a carefully planned murder:

Owen Jennison sat grinning in a water stained silk dressing gown. A month's growth of untended beard covered half his face. A small black cylinder protruded from the top of his head. An electric cord trailed from the top of the cylinder and ran to a small wall socket.

The cylinder was a droud, a current addict's transformer.

It was a standard surgical job. Owen could have had it done anywhere. A hole in his scalp, invisible under the hair, nearly impossible to find even if you knew what you were looking for. Even your best friends wouldn't know, unless they caught you and the droud plugged in. But the tiny hole marked a bigger plug set in the bone of the skull. I touched the ecstasy plug with my imaginary fingertips, then ran them down the hair-fine wire going deep into Owen's brain, down into the pleasure center.

He had starved to death sitting in that chair.

Consider the details of the hypothetical murder. Owen Jennison is drugged no doubt—an ecstasy plug is attached—He is tied up and allowed to waken. The killer then plugs Mr. Jennison into a wall. A current trickles through his brain, and Owen Jennison knows pure pleasure for the first time in his life.

He is left tied up for, let us say, three hours. In the first few minutes he would be a hopeless addict.

No more than three hours by our hypothesis. They would cut the ropes and leave Owen Jennison to starve to death. In the space of a month the evidence of his drugging would vanish, as would any abrasions left by ropes, lumps on his head, mercy needle punctures, and the like. A carefully detailed, well thought out plan, don't you agree?

The readiness to believe that artificial stimulation of the brain can evoke such intense and irresistible pleasures reveals more about our desires than about our brain. Routtenberg and Lindy (1965) did demonstrate that some rats actually starved themselves to death because they continued to stimulate their brains rather than eat. However, one can be terribly misled by the popular accounts of this experiment. In the actual experiment, rats with electrodes implanted in rewarding brain structures were given only one hour a day to press a lever for food. It was necessary for them to eat during that hour in order to stay alive. After the rats were on this feeding schedule for a period, they were given a second lever that offered brain stimulation as a reward. Some of them spent so much time on this second lever that they did not receive sufficient food to keep them alive until the next day's hourly session. This is quite different from the picture most people have in mind about what took place. In the special conditions of a brief test designed to emphasize the controlling power of brain stimulation, some of the rats were apparently not able to anticipate the consequences of choosing the brain stimulation lever. Under conditions providing rats with free access to brain stimulation and food, they never starve themselves. In fact, they eat their usual amount of food (Valenstein and Beer, 1964).

Rewarding brain stimulation is not equally compelling for all species. In humans, it does not seem capable of inducing an irresistible, pleasurable experience. Robert Heath, who is probably more experienced than anyone else with the pleasurable reactions brain stimulation can evoke in humans, has commented that it does not seem able to induce a euphoria equal to that produced by drugs (personal commun.). This is

not to deny that patients have reported feeling considerable pleasure during brain stimulation or that they were willing to repeat the experience, particularly after receiving the impression that this was part of the therapeutic program. (See Valenstein, 1973, for a review of the reports of pleasure evoked by brain stimulation in humans.) Brain stimulation has evoked orgasms, but there is a tendency to attach too much significance to this. It is usually overlooked that, as with masturbation, brain stimulation that produces an orgasm does not continue to be as pleasurable afterward.

The emotional state induced in humans by brain stimulation varies with the emotional and physical condition of the patient. (Heath, John, and Fontana, 1968, p. 168) stated that "When the same stimulus was repeated in the same patient, responses varied. The most intense pleasurable responses occurred in patients stimulated while they were suffering from intense pain, whether emotional and reflected by despair, anguish, intense fear or rage, or physical, such as that caused by carcinoma. The feelings induced by stimulation of pleasure sites obliterated these patients' awareness of physical pain. *Patients who felt well at the time of stimulation, on the other hand, experienced only slight pleasure.*" (Italics mine.)

The existence of circuits in the brain that can induce both pleasure and arousal may be telling us something important about neural mechanisms that have evolved to help focus attention, to increase involvement in a task, and to facilitate the consolidation of memories (see discussion in Valenstein, 1973, pp. 40-44). There are speculations that malfunctioning of these reward circuits is responsible for such psychiatric conditions as depression and schizophrenia (see Stein, 1971). Such speculation leads to more research that ultimately will increase our understanding of how the brain regulates behavior. This is very unlikely to be the consequence of the proposals to use brain stimulation to control behavior.

It would be difficult to fabricate a better example of the distortions that can result from a preoccupation with behavior control than that contained in a proposal, apparently seriously

advanced, by Ingraham and Smith (1972). These two criminologists suggested that techniques are available for maintaining a surveillance on paroled prisoners and for controlling their behavior. They propose that implanted devices could be used to keep track of the location of the parolee and his physiological state while remotely operated brain stimulation could deliver either rewards or punishments or it could control behavior in other ways. For example, Ingraham and Smith (1972, p. 42) suggested the following scenario.

"A parolee with a past record of burglaries is tracked to a downtown shopping district (in fact, is exactly placed in a store known to be locked up for the night) and the physiological data reveals an increased respiration rate, a tension in the musculature and an increased flow of adrenalin. It would be a safe guess, certainly, that he was up to no good. The computer in this case, *weighing the probabilities,* would come to a decision and alert the police or parole officer so that they could hasten to the scene; or, if the subject were equipped with an implanted radiotelemeter, it could transmit an electrical signal which could block further action by the subject by causing him to forget or abandon his project."

It is impossible to be certain, but it seems unlikely that anyone would approve such a plan. The more serious problem is the amount of creative energy diverted from the search for realistic solutions to important social problems by this type of thinking. It sometimes seems that difficulties in implementing necessary social changes encourage people to search for solutions in a fantasy world.

Hopefully, it is clear by now that the responses that can be evoked from stimulating discrete brain areas are too variable and affect too many different functions to be useful in behavior-control schemes. The evoked behavior depends on what is going on elsewhere in the brain, individual and species characteristics, and is very much influenced by situational factors. Those who prefer to think only in terms of control may be very disappointed to learn this. Those who think that the basic concern of science is understanding may find it useful to

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be reminded of the complex relationship between brain and behavior.

It is not surprising that biological solutions to social problems have been discussed most frequently in the context of controlling violence. This discussion, and some actual proposals, have taken very different forms. In his address to the American Psychological Association mentioned earlier, Kenneth Clark also stated:

> Given the urgency of the immediate survival problem, the psychological and social sciences must enable us to control the animalistic, barbaric and primitive propensities in man and subordinate these negatives to the uniquely human moral and ethical characteristics of love, kindness and empathy. We can no longer afford to rely solely on the traditional prescientific attempts to contain human cruelty and destructiveness.

> Given these contemporary facts, it would seem that a requirement imposed on all power-controlling leaders, and those who aspire to such leadership, would be that they accept and use the earliest perfected form of psychotechnological, biochemical intervention which would assure their positive use of power and reduce or block the possibility of using power destructively. It would assure that there would be no absurd or barbaric use of power. It would provide the masses of human beings with the security that their leaders would not sacrifice them on the altars of their personal ego (Presidential Address, American Psychological Association, 1971).

Undoubtedly Kenneth Clark is seriously concerned about possible misuse of the enormous capabilities for destruction that exist. His speech and the types of solutions he proposes make it apparent that he has been greatly influenced by the experiments interpreted as revealing discrete neural circuits regulating aggression. Stripped to its essentials, his proposal appears as a modern variant of phrenology, a belief that the brain is organized into convenient functional systems that conform to our value-laden categories of behavior. Clark seems to believe that we need only to exorcise those critical regions of the brain that are responsible for undesirable behavior, or to suppress them biochemically, and goodness will dominate. Mankind will be saved by a "goodness pill." The great impact of the many distorted descriptions of the power of brain control

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techniques becomes especially evident when even social scientists accept the questionable hypotheses that wars are mainly caused by man's animal-like aggressive tendencies and that biological intervention offers a practical way to prevent them. Clark has not suggested any specific biological intervention, so it is not possible to discuss his proposal in any detail. The situation is different with the proposal advanced by Vernon Mark and Frank Ervin.

Mark and Ervin (1970) stressed the magnitude of the problem of violence in the United States and the belief that a biological approach can make a significant contribution toward finding a solution. The following are typical of a number of statements from their book.

"Violence is, without question, both prominent and prevalent in American life. In 1968 more Americans were the victims of murder and aggravated assault in the United States than were killed and wounded in seven-and-one-half years of the Vietnam War; and altogether almost half a million of us were the victims of homicide, rape, and assault."

They introduced their book (1970) with the Preface that "We have written this book to stimulate a new and biologically oriented approach to the problem of human violence." In the foreword to the book, William Sweet, a neurosurgeon affiliated with Harvard University and the Massachusetts General Hospital and a frequent collaborator of Mark and Ervin, expressed "the hope that knowledge gained about emotional brain function in violent persons with brain disease can be applied to combat the violence-triggering mechanisms in the brains of the non-diseased." Clearly, a biological solution to the problem of violence is sought.

Mark and Ervin suggested that abnormal brain foci in the amygdala are responsible for a significant amount of violent crimes. They believe that these abnormal foci often respond to internal and external stimuli by triggering violent behavior. Mark and Ervin have implanted stimulating electrodes in patients that display a history of episodic violence and claim to be able to locate the "brain triggers" by determining the area

from which violent behavior can be evoked. The treatment consists of destroying the area believed to be responsible for the abnormal behavior.

The relevance of temporal lobe structures for aggressive behavior can be traced back to the seminal studies of Klüver and Bucy (1939), although there were several earlier reports that contained similar observations (for example, Brown and Shäfer, 1888; Goltz, 1892). Most investigators now believe that the temporal lobes and particularly the amygdala nuclei play an important, although complex, role in the expression of aggression, but Klüver and Bucy and all subsequent investigators have emphasized the very many different behavioral changes that follow destruction of this brain region in animals (see Valenstein, 1973, pp. 131-143).

In addition to a "taming" of monkeys (and other animals) after temporal lobe ablation, hypersexuality, increased orality, and a so-called psychic blindness[1] have also been observed. Others have emphasized the emotional "flatness" of the amygdalectomized animal (e.g., Schwartzbaum, 1960). The behavior changes may take very different forms, even diametrically opposite expression, under different circumstances. Amygdalectomized monkeys may become less aggressive toward man, but as Rosvold, Mirsky, and Pribram (1954) reported, the changes in dominance patterns between animals may be more dependent on the history of their social interactions than on the particular brain area destroyed.

Arthur Kling and his colleagues have recently reported even more striking evidence of the fallacy of describing complex change in response tendencies by such shorthand expressions as "increased tameness" (Kling, Lancaster, and Benitone, 1970; Kling, 1972). Kling captured and amygdalectomized wild monkeys in Africa and on Caijo Santiago near Puerto Rico. Control monkeys that were captured and released rejoined their

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[1] "Psychic blindness" refers to a loss of higher integrative visual functions rather than to a loss in visual acuity.

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troupe although some initial fighting was necessary. Before they were released, the amygdalectomized monkeys seemed tamer when approached by the experimenters, but when released into their own troupe they were completely unable to cope with the complexities of monkey social life. The behavior of the amygdalectomized monkeys was often inappropriate. Sometimes they displayed aggression toward dominant animals, a trait never exhibited before. In not too long a period, all the amygdalectomized monkeys either were driven from or re-treated out of the troupe and eventually either died of starvation or were killed by predators. These observations demonstrate the multiplicity of behavioral changes that usually occur following brain lesions and the dependency of these on environmental conditions. In this context, it is interesting that the compulsive sexual mounting commonly observed in amyg-dalectomized monkeys housed in the laboratory was not seen under natural conditions.

The results of amygdalectomy in humans have been less systematically studied. These operations have been performed on patients exhibiting aggressive, hyperkinetic, and destructive behavior, usually (but not always) accompanied by temporal lobe epilepsy. While hypersexuality and orality have been observed to occur postoperatively in humans, most neurosur-geons claim these symptoms are rare and when they occur they subside after several months (see Valenstein, 1973, pp. 209-233, for a review of the clinical literature). Although "psychic blindness" has not been reported, there exist only a few serious studies of intellectual changes following amygdalectomy in humans. In one study, Ruth Andersen (1972) tested 15 patients after amygdalectomy, and even though 13 of them had undergone only unilateral operations, she reported evidence of a loss of ability to shift attention and respond emotionally. Anderson (1972, p. 182) concluded, "Typically the patient tends to become more inert, and shows less zest and intensity of emotions. His spontaneous activity tends to be reduced and he becomes less capable of creative productivity.

"With these changes in initiative and control of behavior, our

patients resemble those with frontal lesions. It must be pointed out, however, that the changes are very discrete and there is no evidence of serious disturbance in the establishment and execution of their major plans of action.

"Presumably he will [function best] in well-structured situations of a somewhat monotonous and simple character."

Typically, amygdalectomy in humans involves destruction of an appreciable proportion of this structure. For example, Heimburger, Whitlock, and Kalsbeck (1966) and Balasubramaniam, Kanaka, and Ramamurthi (1970) estimated that they had destroyed more than 50 percent of the amygdala on each side. In view of the animal literature and Ruth Andersen's observations, one might suspect that had adequate postoperative testing been generally used, intellectual and emotional deficits would have been detected more often. Mark and Ervin (1970, p. 70) implied that their lesions need not be large because of the use of stimulating electrodes to locate the discrete focus that is triggering the violence. They argued that postoperative deficits would be minimized by the smaller, more selective stereotaxic lesions their technique makes possible. For example: "tiny electrodes are implanted in the brain and used to destroy a very small number of cells in a precisely determined area. As a surgical technique, it has three great advantages over lobectomy: it requires much less of an opening in the surfaces of the brain than lobectomy does; it destroys less than one-tenth as much brain tissue; and once the electrodes have been inserted in the brain, they can be left without harm to the patient until the surgeon is sure which brain cells are firing abnormally and causing the symptoms of seizures and violence."

It is important, therefore, to examine critically the validity of the claim that electrical stimulation is a reliable means of locating a "brain trigger of violence."

A few years ago, while studying the elicitation of behavior by hypothalamic electrodes, we noticed an interesting trend (Cox and Valenstein, 1969). In each of the rats we had implanted two electrodes, one on each side of the midline, but usually not

symmetrically placed. We observed that in a number of animals the same response was evoked from very different placements, whereas in other animals either different or no specific behavior was elicited from electrodes that often seemed to be in the same locations (fig. 7). We concluded that within certain anatomical limits, a "prepotent response" tendency of the animal (Valenstein, 1969) appeared to be a more important determinant of the behavior evoked than the exact location of the electrode in the brain.
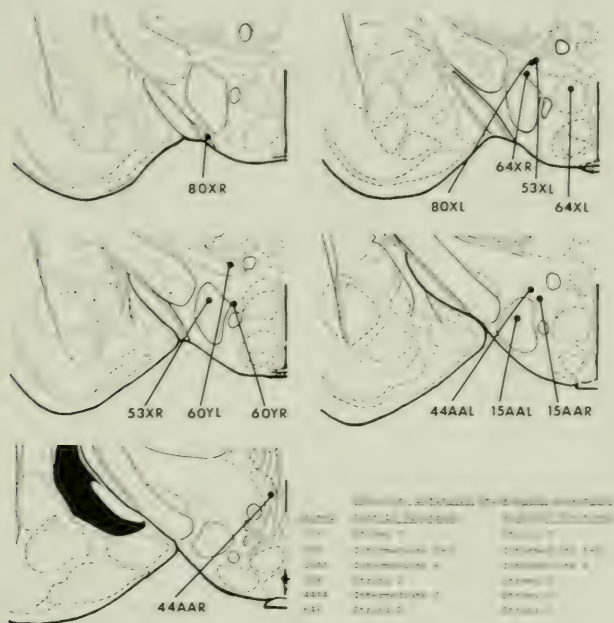

FIG. 7. Illustration of different anatomical locations for two electrodes that evoked the same behavior in a given animal. (Data from Valenstein, Cox, and Kakolewski, 1970. Brain diagrams from König and Klippel, 1963.)

Many were skeptical of our conclusion and cited examples from the literature or from their own laboratory experiences that demonstrated that two electrodes could evoke different behaviors in the same animal. We had never denied this, but had argued that many electrodes evoke states that are sufficiently

similar, yet not specifically identifiable, so that the stimulated animal's behavioral characteristics become a major determinant of the effects produced by stimulation. Additional information has been accumulating supporting our impression. In a recent study using monkeys, it was noted that drinking was elicited initially in some by only a few electrodes, but over time an increasing number of electrodes situated at different brain sites gained the capacity to evoke drinking. Stimulation at an equally varied distribution of sites in other monkeys did not evoke drinking. Some monkeys seem to respond to brain stimulation at many different sites by drinking, whereas others do not (Bowden, Galkin, Rosvold, In press). A similar conclusion may be drawn from an earlier study by Wise (1971) in which rats were implanted with electrodes capable of being moved up and down within the brain (fig. 8). It was found that in some rats eating and drinking were continuously evoked as the electrode was advanced over a large dorsoventral portion of the hypothalamus, but in other rats, these behaviors were not observed in response to stimulation at any site (fig. 9).
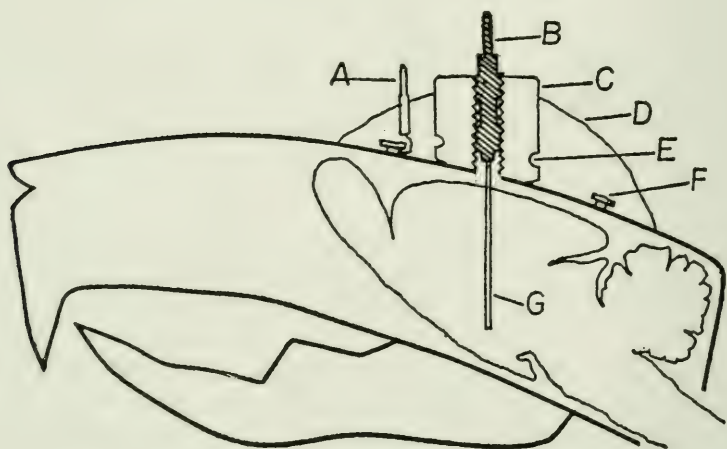

FIG. 8. Sketch of an electrode assembly that can be raised and lowered in the animal's brain. (See Wise, 1971, for details.)

Panksepp (1971, p. 327) has also provided information that supports our "prepotency hypothesis." He has studied the elicitation of mouse-killing responses in rats and has concluded that
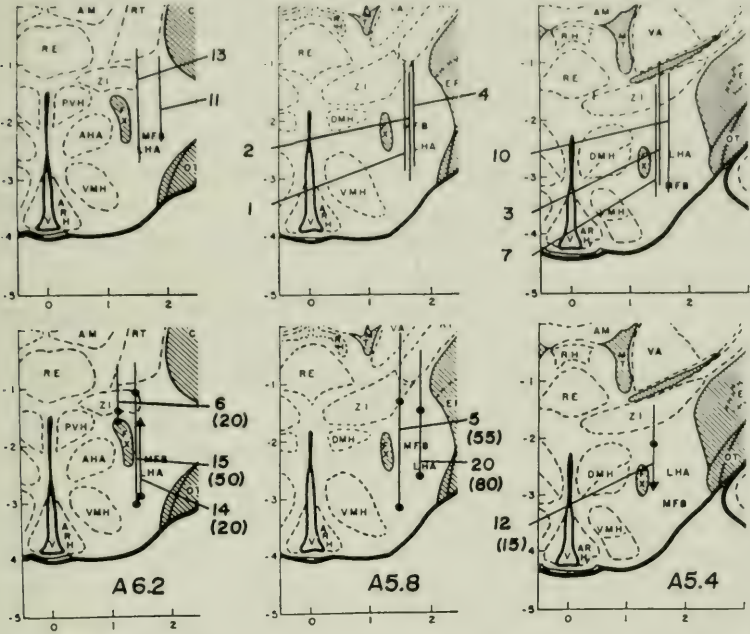

FIG. 9. Path of electrodes used to explore brain for regions evoking eating and drinking. Electrodes were advanced in 0.5 mm. steps descending along the path of the tract. Upper sections show paths of electrode penetrations that did not evoke eating or drinking. In lower sections, both eating and drinking were evoked from all positions between upper and lower circles. Each electrode was placed in a different animal. (See Wise, 1971, for more details.)

the ability to elicit mouse-killing by stimulating the brain of a rat ". . . interacted with the behavioral typology of individual animals, animals normally inclined to kill mice were more likely to kill during hypothalamic stimulation than nonkillers. Thus, the electrically elicited response was probably not determined by specific functions of the tissue under the electrode but by the personality of the rat."

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In regard to humans, Kim and Umbach (1973) reported the effects of stimulating the amygdala of aggressive and nonaggressive patients. They concluded that during amygdala stimulation of aggressive patients "aggressiveness increased, whereas no aggressive reaction was observed in non-violent cases. Thus the amygdaloid complex seems not to be specific for anxiety alone or for aggression alone, and shows no specificity of the subnuclei for these emotional states."

There is little reason, therefore, to believe that brain stimulation is a reliable technique for locating discrete foci that trigger violence even if such foci exist. In the violence-prone patients sent to Mark and Ervin, violence can be triggered by a great number of brain stimulation sites and probably also by a pinch on the skin. The ability of stimulation techniques to ferret out a "critical focus" is far from what it has been touted to be. Indeed, the fact that Mark and Ervin found it necessary to make bilateral lesions to produce any significant effect strongly suggests that no "critical focus" was found. Also supporting this interpretation is the fact that the bilateral lesions are usually made progressively larger until the desired behavior change is believed to have been achieved. Although Mark and Ervin have presented their approach very seductively by implying that they can locate and eliminate small and discrete "brain triggers of violence," in actual practice they seem to be performing "standard" bilateral amygdalectomies.

There is little doubt that there are well-documented cases where the onset of assaultive behavior can be traced to temporal lobe damage. There is also little doubt that there are cases where, by all reasonable standards, surgery has led to considerable improvement in behavior (Gloor, 1967). There has, however, been a gross exaggeration of the amount of violence that can be attributed to brain pathology. The evidence presented by Mark and Ervin is extremely weak. It consists mainly of a recitation of parallel statistics on the numbers of murders, rapes, assaultive acts, automobile accidents, and assassinations, on one hand, and the number of cases of epilepsy, cerebral palsy, mental retardation, and other indica-

tions of brain damage, on the other. Not only are no causal connections established, but the statistical evidence does not support the conclusion that the correlation of brain damage and violence is high.[1] Mark and Ervin have also bolstered their general argument by implying that brain pathology was the cause in such dramatic and violent incidents as the Charles Whitman shooting from the University of Texas tower.[2]

Totally neglected in their description was Whitman's personal history, which could readily have provided an explanation for his violence without any brain pathology. Nor was there any mention that Whitman's carefully laid plans did not conform to the pattern of sudden, unprovoked, episodic violence that Mark and Ervin have described as characteristic of those with abnormal brain foci. It may be relevant to point out that according to the newspapers, Whitman's brother was shot to death in a barroom dispute not too long ago. Is it likely that a temporal lobe tumor was the cause here, too?

There is a danger that the frustration produced by the inability to effectively reverse the accelerating rate of violence will cause those whose minds run toward simplified behavior-control schemes to accept the delusion that biological solutions are available for what are primarily social problems. The varying amount of violence prevalent at different times and in different societies makes it clear that violence is primarily a social

[1] The older neurological and psychiatric literature often contained statements that epileptics, particularly temporal lobe epileptics, are prone to violence. Most neurologists today refute the earlier figures. Current estimates of the incidence of violence among epileptics ranges between 1 and 4 percent and if corrections are made for age (onset of temporal lobe epilepsy is later than for other epilepsies) the relationship is no higher for the temporal lobe subgroup. Rodin (1973) induced seizure in 150 epileptic patients using the EEG activating drug, bemigride. He reported that there was no incident of aggressive behavior during or after the psychomotor automatisms that occurred in 57 of the patients. He argued that the often-reported relationship between aggression and psychomotor epilepsy has been exaggerated.

[2] It had been frequently stated that a cancerous tumor (glioblastoma multiforme) was situated in the amygdala. Actually, because of the mishandling of the brain at the time of autopsy, the location of the tumor was never clearly established (Frank Ervin, personal commun.).

phenomenon. If drug-related crimes are excluded, most of the present upsurge in violence can be related to the rejection of previously accepted social roles, the large numbers of people who do not believe they have a vested interest in the stability of our society, and the increasing belief that our institutions cannot or will not initiate the changes that are needed. These are not easy problems to remedy, but we will surely be in serious trouble if a number of influential people become convinced that violence is mainly a product of a diseased brain rather than of a diseased society.

PSYCHOSURGERY

The current controversy over what has been called the "resurgence of psychosurgery" places a responsibility on those of us studying the brain and behavior—whether or not we welcome the opportunity—to offer some light in the midst of all this heat. Anyone who has participated in a public discussion of this issue realizes that psychosurgery is one of those topics on which most people prefer to have one soul-satisfying emotional outburst rather than attempt to draw conclusions from very complex and often conflicting data. While I have nothing against emotional catharsis, there is an obligation to examine the logic of the arguments and the relevant evidence as impartially as possible, if we are to make a contribution to something besides our own psychological well-being. Some of the political and social arguments that have been introduced have aroused such passion that people are forced to take sides on these issues and in the process forget that there may be a patient in desperate need of help. It is possible to make only a few remarks and I offer these in an effort to set the stage for some constructive dialogue by placing the problem in perspective. The serious ethical and legal questions concerning in-formed consent, adequate review of experimental medical procedures, and operations on children or those committed to psychiatric and penal institutions cannot be discussed here (see Shapiro, 1974, and Valenstein, 1973).

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No discussion on this topic would be complete without at least one person arguing against psychosurgery by reminding us that the brain is the seat of our personality, humanity, creativity, capacity to learn, to experience emotion, and even of our soul.[1] It is certainly true that if we remove the brain all of these capacities will be lost, with the possible exception of the soul. I do not want to appear facetious or to denigrate these human qualities, but I want to emphasize that we must talk about particular parts of the brain and the functions that are regulated by these parts. It is well known that many people have had localized brain tumors removed with little, if any, detectable loss in these human capacities.

It is often argued that psychosurgery is unique in that healthy tissue is destroyed for a presumed therapeutic purpose. In truth, however, psychosurgery is really not that unique in this regard. There are several medical procedures that involve the destruction of healthy tissue in order to accomplish some therapeutic advantage. For example, removal of a normal endocrine gland to arrest some pathological process is not uncommon. Unquestionably, there are important differences between removing an endocrine gland, where replacement hormonal therapy is possible, and destroying part of the brain, but there also exist procedures other than psychosurgery that involve destruction of normal brain tissue. It is instructive to consider a few such examples.

Dr. Irving Cooper of St. Barnabas Hospital in New York has done more than 10,000 brain operations on patients suffering from such movement disorders as Parkinsonian tremors, various types of spasticity, and choreoathetosis. While not everyone concurs, Cooper (1969) reported a high percentage of success.

[1] For example, the preamble to a bill controlling psychosurgery passed in June, 1973, by the Oregon State legislature (Senate Bill 298) reads: "Whereas it is acknowledged that the human brain is the organ which gives man his unique qualities of thought and reason, personality and behavior, emotion and communication. And, indeed, is that unique structure importing to man his soul and ethical being; and

"Whereas these things being so, the free and full use of brain is the absolute and inalienable right of each individual, a prerequisite for making choices, possessing insight and judgement, and in health providing for the exercise of citizenship . . ."

In all likelihood, Cooper destroyed healthy brain tissue (in the ventral thalamus or basal ganglia) as he freely admits in his writings. It is important to appreciate that in many instances there is some loss of function unrelated to the regulation of movement that is incurred. For example, in one review Cooper and his colleagues (Cooper et al., 1968) pointed out that following surgery 58 percent of the patients suffer "mild," and 28 percent "moderate," deficits in speech articulation, phonation, and even the selection of appropriate words. The danger of such undesirable side effects does not necessarily rule out a therapeutic procedure. The risks must be weighed against the possible benefits.

To cite a different example. Many cases of temporal lobe epilepsy are classified as idiopathic—that is, of unknown origin. Indeed, Dr. Wilder Penfield of the Montreal Neurological Institute wrote that he believed that in a number of instances the basic disorder may actually exist in some subcortical region and be projected to the temporal lobe. Nevertheless, there are many people with excellent credentials and extensive experience who would agree that the removal of a restricted part of the temporal lobe has helped patients with otherwise intractable episodes of seizures, although here too undesirable side effects— in some cases serious—are not unknown.

In other cases of intractable epilepsy the cutting of the corpus callosum, the most extensive fiber connections between the two sides of the brain, has significantly decreased the incidence of seizures according to Drs. Bogen and Vogel of the California College of Medicine. No one believes that the corpus callosum in these patients was not perfectly normal before surgery. Here too there were deficits produced by the surgery. Sperry and his colleagues, for example, have demonstrated striking deficits in these "split-brain" people, but it takes special testing to reveal them (see Gazzaniga, 1970). Postoperatively, the patients function quite well in normal life situations, certainly much better than when they were plagued by a number of grand mal seizures every day.

Admittedly these surgical procedures are controversial and

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drugs have decreased the need for them. It should be noted, however, that many would argue that these surgical techniques are still very helpful for the elimination of some intractable symptoms and that a loss-benefit analysis would justify their use. Therefore, with respect to the issue of destroying healthy tissue, psychosurgery should not be thought of as a unique therapeutic practice. It is more realistic to view it as one end of a continuum differing mostly on the clarity of the diagnosis rather than the treatment.

It is true that as of now there is virtually no reliable evidence linking psychiatric disorders to brain pathology.[1] It is important to note, however, that there are few brain scientists prepared to rule out the possibility that significant relationships between psychiatric condition and brain abnormalities may be found in the future. One of the difficulties thus far encountered in the search for a relationship is that evidence of pathology in the nervous system is much more subtle than it is in other organs. It certainly is possible that functional abnormalities in the brain of psychotic patients can never be detected by the relatively low magnification of the light microscope. It has been reported that the electron microscope has revealed significant defects in the fine aborizations of neurons in the brains of some mental defectives. It is possible that the greater degree of magnification afforded by the electron microscope may reveal structural abnormalities in selective regions of the brains of some psychiatric patients.

Unless one argues for the independence of mind and body, the possibility of structural or biochemical abnormalities cannot be ruled out. It should be noted that even if regional brain abnormalities are found, it is not necessary to assume that these were the initial cause of the psychiatric disorder. Abnormal

[1] Dr. Fred Plum's recent observation that "schizophrenia has been the graveyard of many neuropathologists" refers to the fact that a large number of early pathologists wasted much of their professional lives pursuing false leads. These leads could not be substantiated by others or were shown to be brain artifacts resulting from the deteriorated physical condition of long term institutionalized patients (see Kety and Matthysse, 1972).

brain functioning could be a by-product of abnormal behavior produced by environmental contingencies. Nevertheless, once produced, such brain functioning could play a major role in maintaining abnormal behavior, emotionality, and thought processes. We certainly do not object to this type of reasoning when applied to disorders that we label psychosomatic. When a substantial number of neuroscientists believe that brain abnormalities, perhaps of a biochemical nature, will eventually be linked to some psychiatric disorders, measures that close the door to future investigation of this possibility should be discouraged.[1]

Still another argument raised is that the rationale for psychosurgery, that is, the physiological evidence that justifies the procedure, is very primitive. This is true enough and I have discussed the problem in detail elsewhere (Valenstein, 1973). We should observe, however, that a number of medical treatments is based on the empirical evidence that they work despite the fact that understanding of the physiological mechanisms responsible for their action are not available. If we demanded a good rationale for all medical treatment we would not even use aspirin, not to mention psychopharmacological drugs and electroconvulsive shock treatment. (Incidentally, despite considerable criticism of the possible overuse of electroconvulsive treatment and its poorly understood mechanisms for inducing change, the majority of psychiatrists maintain that it is still the most effective way of arresting some cases of very severe depression.)

Judging from accounts in the popular news media, the issue that has caused the most concern is the charge that psychosur-

[1]Of interest here is a recent poll of the Society for Neuroscience, an organization that includes among its members most of the leading brain scientists in this country. Of the 873 respondents, 74% (16% disagreed and 10% had no opinion) expressed the belief that psychosurgery should be available to patients suffering from incapacitating mental disorders provided adequate safeguards are taken. A great majority (76%) of the members felt, however, that a commission should be established "to promulgate guidelines for selecting and evaluating patients, for certifying that there is a recognized functional disorder, for determining that psychosurgery is an appropriate last resort, for obtaining informed consent and for follow-up and record keeping."

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gery may be used as a political instrument to control people, particularly so-called militant blacks. These charges have been accepted as true and repeated by many people who have made no effort to check the facts. My own view, after carefully surveying the literature and doing some direct checking, is that the charges cannot be substantiated and that they were really demagogic attempts to add emotional fire to the issue and to secure political allies.[1] It is clear that we have to be vigilant and monitor carefully the practices in state and private institutions where there may be disproportionate representations based on race, social class, or sex. As real and as serious as that problem may be, however, it is quite different from some of the charges we have been hearing. It should be noted that a substantial proportion of the 500 to 600 psychosurgical patients operated on in the United States each year are not institutionalized, but are private patients referred by psychiatrists.

In the minds of many, psychosurgery is thought of as a behavior-control technique of potentially wide applicability rather than as an experimental therapeutic procedure for intractable psychiatric disorders. This belief has had a very significant influence on legislation presently being considered. For example, in the proposed federal legislation (H.R. 6852)

[1] To the best of my knowledge, the person most responsible for this belief is the psychiatrist Peter Breggin. Breggin has charged that "these brain studies are not oriented toward liberation of the patient. They are oriented toward law and order and control—toward protecting society against the so-called radical individual." In his statement attacking psychosurgery, which was read into the *Congressional Record* (February 24, 1972, vol. 18, no. 26), Breggin implied that Dr. O. J. Andy, a Mississippi neurosurgeon, concealed that he was operating mainly on blacks. This and similar charges have been repeated by many people as well as in such magazines as *Ebony* (Mason, 1973) apparently without troubling to check the facts. However, in answer to my inquiry, Dr. Andy wrote that of the approximately 40 psychosurgical operations he has performed, only 5% (i.e., 2 cases) were black. At a symposium on psychosurgery at the 1973 American Psychological Association Meeting in Montreal, Dr. William Scoville, the outgoing president of the International Psychosurgical Association, stated that he has never performed psychosurgery on a black person. The speculation by Mark, Sweet, and Ervin (1967) that the more violent participants in a riot may have some brain pathology has undoubtedly caused much anxiety about future applications. Nevertheless, their psychosurgical patient population does not reflect any racial bias.

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outlawing psychosurgery these procedures are defined as brain surgery for the purpose of:

"(A) modification or control of thoughts, feelings, actions, or behavior rather than the treatment of a known and diagnosed physical disease of the brain;

"(B) modification of normal brain function or normal brain tissue in order to control thoughts, feelings, action, or behavior"

Similar wording can be found in other proposed legislation or legislation that has already been passed. Clearly the concern that these techniques will be used to control people has provided a good part of the motivational impetus behind such legislation. It is understandable that black congressmen and women are among the leading supporters of the above legislation. Apparently, they have been convinced that psychosurgery is a technique for controlling behavior that has been or is likely to be selectively used against one segment of the population. It is most important that precedent-setting legislation aimed at curtailing experimental medical procedures be considered carefully and not hastily framed in response to a distorted representation of the problem.

This critique of many of the common arguments against psychosurgery should not be construed as my support for these surgical procedures. My reasons for presenting this point of view are twofold. On the one hand, I believe that if psychosurgery is criticized on the wrong grounds the legislative remedies may take a form that would establish a dangerous precedent. Also, a criticism of irrelevant arguments or unsubstantiated charges can help to focus our attention on what should be the main issue, namely, Can destruction of a part of the brain be justified on therapeutic grounds? This question is easier to ask than to answer. Even if all the data on the consequences of a particular psychosurgical procedure were in agreement and their meaning unambiguous, it would still be possible to reach opposite conclusions because of personal weights assigned to gains and losses in different capacities. Is a flattening of emotional responsiveness, for example, balanced by freedom from a crippling anxiety?

It is not possible for me to present any firm conclusions, let alone to substantiate them, on the approximately one-dozen different brain operations that could be called psychosurgery. Raising some of the main problems that will have to be faced in evaluating any psychosurgical procedure may serve some useful purpose. To begin, we have to face the likelihood that the results of any brain operation probably will always contain an element of unpredictability that will not be completely eliminated by any increased technical precision. This is true in part because the ramifications of destroying any part of the brain must depend upon the total personality of the patient, or if you prefer, on the total neuronal context that must mediate the impact of destruction of any one part of the brain. Moreover, there is usually some compensation for loss in function following brain damage, but the amount of compensation varies with individuals for a great number of reasons we cannot go into at this time.

Another problem in evaluating psychosurgery is that the available evidence leaves much to be desired. In the first place, most of the testing of patients following psychosurgery was done at a time when the patient population and the surgical procedures were different from those that exist today. The older prefrontal lobotomy procedures destroyed much larger brain areas than do the current so-called fractional operations. Although most of the older operations involved rotating surgical knives inside the brain in order to disconnect large areas of the prefrontal cortex, present-day techniques may limit destruction to an area 3 to 5 mm. in diameter. There is also little doubt that the more modern methods of stereotaxic surgery make it possible to reach specific brain targets with much more precision than was previously possible.

No purpose is served by reviewing in detail the results of the older prefrontal lobotomy procedures. The results were extremely variable and one can without difficulty find evidence on both sides of the controversy. There is evidence in the literature demonstrating a blunting of emotional responsiveness, lowering of performance on at least some parts of IQ tests, an

inability to maintain goal-directed behavior, the triggering of epileptic seizures, and other neurological problems following prefrontal lobotomy. There are also a number of studies that reported significant psychiatric improvement following the operations, no IQ loss, and an increased ability to hold a job. Some of the studies that reached this positive conclusion involved relatively long-term follow-ups and some, such as those conducted by the Connecticut Lobotomy Committee or the British Board of Control Study, included substantial samples of patients (Moore et al., 1948). The Columbia-Greystone study, which involved more than 50 participating investigators and a battery of 35 psychological tests (selected from a list of more than 100 that were considered), concluded that there was no evidence that topectomy (one type of prefrontal operation) produced any permanent loss in learning ability, memory, creativity, imagination, intellectual achievement, social or ethical attitudes, or even sense of humor (see Mettler, 1949, 1952; Landis, Zubin, and Mettler, 1950). These studies can all be criticized on various methodological grounds; the test instruments were probably insensitive to important changes in behavioral capacities, and the estimates of improvement often gave exaggerated weighting to the elimination of behavior troublesome to the hospital staff or society in general while placing considerably less emphasis on the qualitative aspects of the postoperative adjustment level.

While we can learn much from examining the older prefrontal lobotomy literature—particularly in respect to methodological points in the way such studies should or should not be conducted—it is not possible to apply specific conclusions to the brain operations performed today. Very different brain areas are often involved, even where the surgery is still directed at prefrontal areas. There are fewer studies reporting results following selective damage to limbic and hypothalamic structures. It is probably safe to conclude that the added precision of the newer operations has resulted in many fewer instances of gross behavioral deterioration, or neurological side-effects such as epilepsy. However, our information about the emotional and

intellectual changes produced by the newer psychosurgical procedures is very inadequate.

Neurosurgeons have neither the training nor the time to conduct the type of studies needed to evaluate adequately the changes produced by their brain operations. Postoperative changes are usually reported in gross terms listing percentages of patients exhibiting different degrees of improvement in poorly defined categories ranging from "completely cured" to "no change." There are few examples where postoperative evaluative tests were designed to measure changes in those capacities that animal studies have emphasized as likely to be altered. Indeed, many neurologists and neurosurgeons have displayed an amazing "tunnel vision" toward animal studies. They have been quick to see clinical applications in animal studies, but often quite blind to the results that should have cautioned them against the operation and influenced their evaluative procedures. A few examples are offered to illustrate this point.

There is some familiarity with the circumstances that encouraged Egas Moniz, the Portuguese neurologist and Nobel laureate, to initiate prefrontal lobotomy. It will be recalled that at the International Neurology Congress in London in 1935 Carlyle Jacobsen presented his results on the behavior changes in chimpanzees following destruction of their frontal lobes. Prior to the operation, one of the chimpanzees—the now-famous Becky—had a temper tantrum every time she made a mistake in the testing situation. After frontal lobe surgery, however, she showed no evidence of emotional disturbance under similar circumstances. Moniz was sitting in the audience, and according to John Fulton, the session chairman: "Dr. Moniz arose and asked if frontal lobe removal prevents the development of experimental neurosis in animals and elimi-nates frustrational behavior, why would it not be feasible to relieve anxiety states in man by surgical means." *The main thrust of Jacobsen's presentation, namely, that the operated animals were no longer able to perform certain problem-solving tasks (particularly those involving delayed responses) was*

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ignored. Within three months, Moniz had persuaded his neurosurgical colleague, Almeida Lima, to operate on their first patient.

Anterior cingulotomy is another psychosurgical procedure used by several surgeons today. Here, too, a careful reconstruction of the history reveals a striking "tunnel vision." John Fulton's description of the animal experiments by Wilbur Smith (1945) and Arthur Ward (1948) in a number of influential speeches had a direct influence on the adoption of cingulotomy procedures by a number of people in England, France, and in the United States. Fulton reported that following cingulotomy monkeys became tamer. A closer examination of Ward's description of the postoperative behavior of the monkeys reveals the inadequacy of the term "tameness" to summarize all the changes that occurred. For example, Ward said:

> there is an obvious change in personality. The monkey loses its preoperative shyness and is less fearful of man. It appears more inquisitive than the normal monkey of the same age. In a large cage with other monkeys of the same size, such an animal shows no grooming behavior or acts of affection towards its companions. In fact, it treats them as it treats inanimate objects and will walk on them, bump into them if they happen to be in the way, and will even sit on them. It will openly eat food in the hand of a companion without being prepared to do battle and appears surprised when it is rebuffed. Such an animal never shows actual hostility to its fellows. It neither fights nor tries to escape when removed from a cage. It acts under all circumstances as though it had lost its "social conscience." This is probably what Smith saw and called "tameness." It is thus evident that following removal of the anterior limbic area, such monkeys lose some of the social fear and anxiety which normally governs their activity and thus lose the ability to accurately forecast the social repercussions of their own actions.

Perhaps the most striking example of "tunnel vision" comes from a psychosurgical procedure that involves destruction of the ventromedial hypothalamus in persons diagnosed as pedophilic homosexuals, that is, men who seek out sexual opportunities with young boys. Dr. F. Roeder and his colleagues at the University of Göttingen in Germany received their inspiration while watching a film at another International Neurology Congress, held in Brussels in 1957 (Roeder et al., 1971, 1972).

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Roeder described his response to this film which depicted the hypersexual behavior of cats amygdalectomized by Leon Schreiner and Arthur Kling, "the behavior of male cats with lesions of the amygdalar region in some respects closely approached that of human perversion. The films convinced us that there was a basis for a therapeutic stereotaxic approach to this problem in man." Roeder was referring to work on cats by Arthur Kling which demonstrated that ventromedial hypothalamic lesions eliminated the hypersexuality previously produced by amygdala lesions. Roeder and his colleagues proceeded to make stereotaxic lesions in the ventromedial hypothalamic nucleus in man. Based on experience with a relatively small patient population studied in a cursory way, Roeder and his associates reached the disquieting if not shocking, conclusion about their surgical procedure that "there is no doubt that experimental behavioral research has afforded us a basic method to eliminate or to control pedophilic homosexuality by means of an effective psychosurgical operation in the area of the sex behavior center." Those of us who study the brain and behavior in animals know of the voluminous literature implicating the ventromedial hypothalamic nucleus in endocrine regulation, appetite, and many other functions. There is also good evidence that irritability and aggressiveness can be produced by lesions in this area. However, once the focus was directed at sexual behavior, the other important behaviors regulated by this brain area were ignored.

Similar comments could be made in reference to a recent report on producing stereotaxic lateral hypothalamic lesions to combat obesity in humans (Quaade, 1974). As Marshall (1974) pointed out in a comment on Quaade's report, the lateral hypothalamus is not specifically involved in "monitoring the energy needs of the organism and transforming such information into an urge to eat." In animals, lateral hypothalamic damage also produces sensory changes leading to inattentiveness to external stimuli and impairment in sexual activation, learning ability, and memory.

A point that apparently has to be made over and over again is

that there are very few parts of the brain that control only one behavior. People studying a given area of the brain may emphasize either control of appetite, aggression, endocrine balance, or sexual behavior, and so forth, depending on their own interests. I have stressed this "tunnel vision" problem because it illustrates the danger of superficial contacts between experimentalists and clinicians. There are many consequences of this lack of communication. Obviously, in some instances, operations should never have been performed. In a great many instances, behaviors and capacities that should have been assessed were completely neglected in the postoperative evaluation of patients. What is needed is not some hastily conceived legislation that may set a precedent hindering all investigations in experimental medicine. We clearly need better controls to protect patients, but it must be recognized that this cannot be accomplished unless more meaningful interactions between research scientists and clinicians are established.

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WHAT SQUIDS AND OCTOPUSES TELL US
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ABOUT BRAINS AND MEMORIES

JOHN Z. YOUNG

FORTY-SIXTH

JAMES ARTHUR LECTURE ON
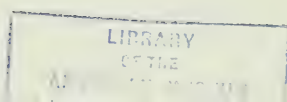
THE EVOLUTION OF THE HUMAN BRAIN

WHAT SQUIDS AND OCTOPUSES TELL US ABOUT BRAINS AND MEMORIES

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JAMES ARTHUR LECTURES ON
THE EVOLUTION OF THE HUMAN BRAIN

Frederick Tilney, *The Brain in Relation to Behavior*; March 15, 1932

C. Judson Herrick, *Brains as Instruments of Biological Values*; April 6, 1933

D. M. S. Watson, *The Story of Fossil Brains from Fish to Man*; April 24, 1934

C. U. Ariens Kappers, *Structural Principles in the Nervous System*; *The Development of the Forebrain in Animals and Prehistoric Human Races*; April 25, 1935

Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders*; May 15, 1936

R. W. Gerard, *Dynamic Neural Patterns*; April 15, 1937

Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull*; May 5, 1938

G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates*; May 11, 1939

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*Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny*; April 26, 1956

*Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man*; April 25, 1957

*David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action*; May 8, 1958

*Charles R. Noback, *The Heritage of the Human Brain*; May 6, 1959

*Ernst Scharrer, *Brain Function and the Evolution of Cerebral Vascularization*; May 26, 1960

Paul I. Yakovlev, *Brain, Body and Behavior. Stereodynamic Organization of the Brain and of the Motility-Experience in Man Envisaged as a Biological Action System*; May 16, 1961

H. K. Hartline, *Principles of Neural Interaction in the Retina*; May 29, 1962

Harry Grundfest, *Specialization and Evolution of Bioelectric Activity*; May 28, 1963

*Roger W. Sperry, *Problems Outstanding in the Evolution of Brain Function*; June 3, 1964

*José M. R. Delgado, *Evolution of Physical Control of the Brain*; May 6, 1965

Seymour S. Kety, *Adaptive Functions and the Biochemistry of the Brain*; May 19, 1966

Dominick P. Purpura, *Ontogenesis of Neuronal Organizations in the Mammalian Brain*; May 25, 1967

*Kenneth D. Roeder, *Three Views of the Nervous System*; April 2, 1968

†Phillip V. Tobias, *Some Aspects of the Fossil Evidence on the Evolution of the Hominid Brain*; April 2, 1969

*Karl H. Pribram, *What Makes Man Human*; April 23, 1970

Walle J. H. Nauta, *A New View of the Evolution of the Cerebral Cortex of Mammals*; May 5, 1971

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János Szentágothai, *The World of Nerve Nets*; January 16, 1973

*Ralph L. Holloway, *The Role of Human Social Behavior in the Evolution of the Brain*; May 1, 1973

*Elliot S. Valenstein, *Persistent Problems in the Physical Control of the Brain*; May 16, 1974

[a]Marcel Kinsbourne, *Development and Evolution of the Neural Basis of Language*; April 10, 1975

*John Z. Young, *What Squids and Octopuses Tell Us About Brains and Memories*, May 13, 1976

[a]Unpublished.

*Published versions of these lectures can be obtained from The American Museum of Natural History, Central Park West at 79th St., New York, N. Y. 10024.

† Published version: *The Brain in Hominid Evolution*, New York: Columbia University Press, 1971.

WHAT SQUIDS AND OCTOPUSES TELL US ABOUT BRAINS AND MEMORIES

NEW TECHNIQUES FOR STUDIES OF THE BRAIN

To reach a better understanding of the human brain we need to develop new ways of thinking and talking about the nervous system in general. All our knowledge of nerve fibers and their synapses proves to be something of a disappointment when we try to explain complex forms of behavior, such as that of man. I have believed for many years that to overcome this difficulty we must try to describe as fully as possible the behavior patterns and the whole nervous system. When I began research, I thought that it might be possible to do this for lampreys and after making some studies went so far as to write what would now be called a research program with this in view. But on further consideration, I decided that both the behavior and structure of the brain of these animals were too difficult to study, mainly for technical reasons. Moreover in 1929, for the first time, I became acquainted with octopuses and squids and quite soon decided that their nervous systems seemed likely to provide sufficient complexity to be interesting and sufficient accessibility for anatomical study and experiment. It is not too much to make the claim that this hope was well founded, as we now have some understanding of all parts of the cephalopod nervous system. We also have a lot of information about their behavioral capacities—at least in the laboratory; less, unfortunately, in their native state in the sea.

It may seem to be a vain and unjustified claim that we understand cephalopod brains so well. Of course, there is an immense amount that we should like to know. But I hope that the effort to substantiate this claim may serve to bring out both the extent and the limitations of our knowledge of all brains, including that of man. It may show how what we mean by "understanding the brain" has changed over the last 50

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years since this research began. This may prove to be quite a useful exercise not only in the history of neuroscience but in the study of the relations of science and technology in general.

We can recognize four major changes of scientific method and capabilities since 1929 that have especially influenced neurology.

1. Reliable methods of recording small changes in electrical activity have become widely available. With these we can follow events in nerves and brains with a very high degree of resolution in time. Resolution in space can also be precise, but is limited to a few places in the brain at a time.

2. Electronmicroscopy has provided us with the power to study the structure and organization of neurons with a very high degree of resolution in space. This, unfortunately, is possible only by accepting very poor resolution in time. We cannot follow changes from moment to moment with the electron microscope.

3. Chromatography provides us with the power to study the microchemical composition of tissues, estimating quantities of substances that are present in very small amounts, though again with rather poor resolution in both space and time. Fluorescence microscopy has also been particularly helpful in the study of the nervous system because of its capacity to reveal selectively the course of tracts containing biologically active amines.

4. Finally, during this period mankind has enormously enlarged his mathematical powers of computation. Computers help us to bring together the vast masses of data provided by other techniques. Besides their help with arithmetical operations, it is even more important that computers have led to great advances in our understanding of the operations of communication and control which, until recently, were considered only by using the language of subjective psychology.

Knowledge of the nervous system has profited from these advances. My own detailed contributions have mostly been in

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humbler fields, using older techniques of histology and psychology. But through developments that we have sponsored in the Department of Anatomy at University College, London, I have been near the beginning of several of these four major new developments of technique and have been able to find helpers in applying them to cephalopods.

THE BRAIN AS A HIERARCHICAL SOMATOTOPIC COMPUTER

Our aim is to try to understand the nervous system as a whole. Let us therefore begin with the last of the new techniques mentioned. Cybernetics can tell us how to think of the brain as a hierarchical computer, somatotopically organized (Arbib, 1972). The idea of hierarchy in the nervous system was introduced by the clinician Hughlings Jackson long ago, and cybernetic analysis shows that it is really an essential feature of any organization that uses much information to accomplish a purpose, whether it be an army or an octopus. Hierarchy allows each level to receive only that part of the information that is relevant for the decisions it must take. This is magnificently illustrated by octopuses (fig. 1). Each of the eight arms carries hundreds of highly mobile suckers and the movements of
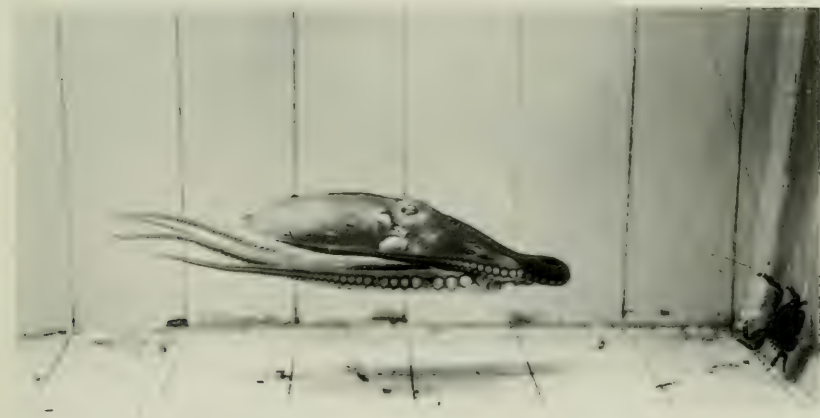

FIG. 1. An octopus swimming forward to attack a crab.

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these, and of the whole arm, are controlled by nerve cells lying in ganglia within the arm. There are altogether 350 million cells in the arms as compared with only 150 million in all the rest of the nervous system (Young, 1971). The suckers are the enlisted men of the cerebral army, and their local nerve cells are the noncommissioned officers. Individual isolated arms are capable of quite complicated coordinated movements, for example acting either to draw objects in or to reject them. These peripheral centers are thus the next layer of members of the hierarchy and can act independently. They are the regiments of the cerebral army, and the nerve cells placed along the center of each arm are the junior officers who control them. They receive information from individual suckers and order them to act in particular sequences.

The brain contains lower motor centers, comparable with our own spinal cord (fig. 2), and these control movements of all the arms when working together and of the mantle, which acts by jet propulsion. Electrical stimulation of these centers will produce movements of the relevant parts, including changes of color by the chromatophores (Boycott and Young 1950; Boycott, 1961). To pursue our analogy we here have regimental and brigade headquarters. They receive relevant information from the arms and send orders to them. However, these centers normally operate under the control of still higher motor centers in the basal supraoesophageal lobes. These basal lobes have structure strikingly like our own cerebellum, but before we can understand their working we must begin to think more carefully about what tasks the nervous system has to do, and what we mean when we say that it sends information, instructions, or commands.

COMMUNICATION AND CONTROL BY THE NERVOUS SYSTEM

Since the last century it has been usual to think of the nerves as agents of communication, following the analogy of telegraph wires. But what do they communicate? Neurophysiologists have been cautious and confused about this ever since the time Des-

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FIG. 2. Longitudinal sagittal section of the brain of an octopus.

cartes spoke of nerves with the analogy of pulling on wires to ring bells or of animal spirits traveling along hollow tubes.

During the last century and the present one, physiologists have mostly described the activity of nerves by using unquestioningly the phrases "nerve impulse" or "action potential," but now we can see that these are rather ambiguous and indeed eva-

sive terms. This will sound like rank heresy, especially coming from me since the giant nerve fibers of the squid have told us more about nerve impulses than any other nerve fibers have done (fig. 3). I came upon them by chance while studying squid ganglia for another purpose. The cells related to them had indeed been seen by Williams in 1909. But there had been no further mention of the cells in the literature, and no one had seen the giant fibers themselves. In 1936 at Woods Hole we were able to prove that these huge channels are nerve fibers and figure 4 shows some of the earliest records of their action potentials. The function of these enormous nerves is to elicit contraction of the sac that produces the propulsive jet. The arrangement ingeniously provides that both sides of the mantle and its nearer and distant parts all contract together (fig. 5).

If the function is so well understood, what do I mean by saying that the concept of an impulse or action potential is ambiguous? What's in a name? In this context of the giant fiber system I agree that it does not matter much. An activity spreads
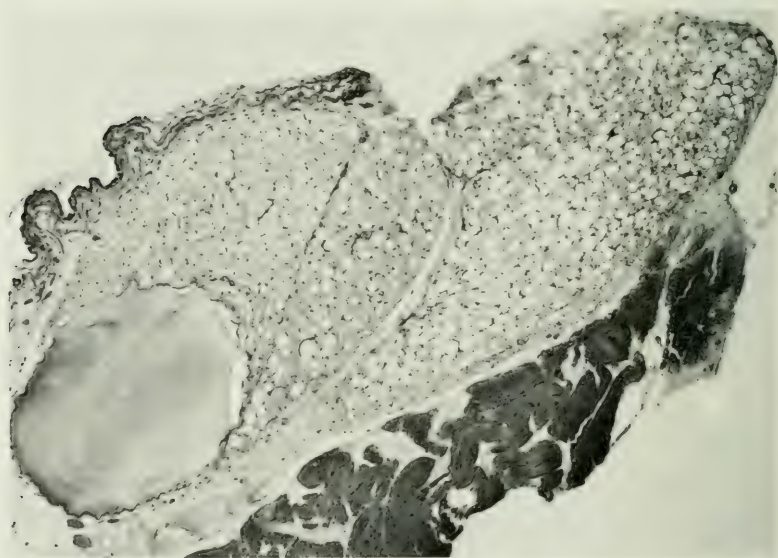

FIG. 3. Transverse section of one of the stellar nerves of a squid. There are many small nerve fibers and one giant fiber.
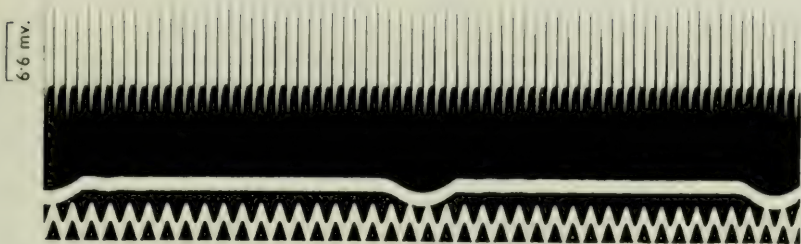
FIG. 4. Oscillograph record of the electrical changes accompanying a sequence of nerve impulses in a squid's giant nerve fiber. The discharge has been set off by placing oxalic acid on one end of the fiber. Note that the impulses are all the same height. The time-markers show 1/5 or 1/100th sec.

along the nerve fibers and we can tell rather precisely how it is initiated by a synapse in the stellate ganglion and propagated to start off a muscular contraction. We can even show that one nerve impulse produces one pulse of the jet, so we can say that the action of single cells in the nervous system produces a particular behavioral act by the whole squid. This is good progress in understanding. We can go further and apply it to mammals where, in a monkey trained to press a lever, single cells of the cerebral cortex show electrical activity before the movement begins (Evarts et al., 1971). Thus we get a good idea of how the nervous system is made up of nerve cells each of which has a distinct function.

This sounds fine and is indeed true. The principle on which all nervous systems are built is that of multichannel communication. Each nerve fiber carries only one sort of message, either inward from a sense organ or outward to produce some action by a muscle or gland. Each fiber thus carries only a small amount of information. To carry large amounts of information inward and to produce varied and subtle behavior, very large numbers of fibers are needed, each having a different "function." The trouble is that in the more interesting parts of the brain we cannot specify what the "function" is. So when we say that when we see red certain nerve fibers from the eye transmit something called nerve impulses we do not really know what we are saying. In what sense do nerve impulses transmit redness?
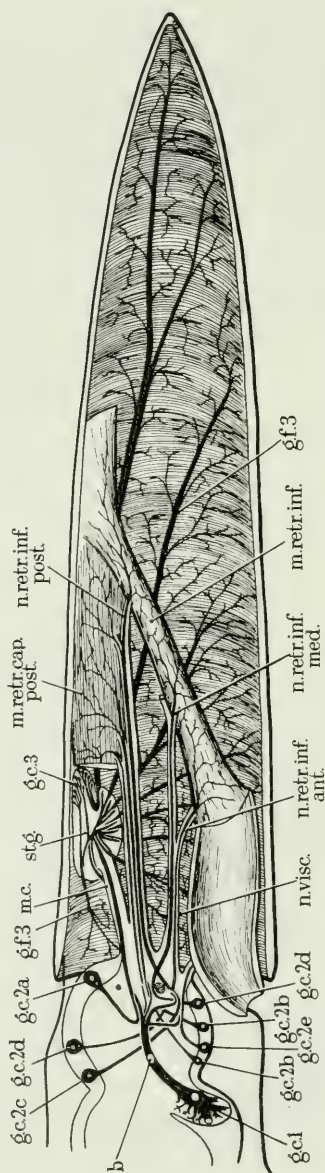
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FIG. 5. Diagram of the giant nerve fiber system of the squid. Three links are involved. gc_1 is the giant cell (one on each side), which is activated by signals from the eyes, statocyst and elsewhere. Nerve impulses pass along its axon and across the bridge, b, so that the two sides always work together. The fiber then branches and makes synaptic contact with the various second-order giant fibers, labeled g.c.2a, 2b,2c, etc. These pass signals to the various muscles that are involved in the jet. The chief of these is g.c.2a, whose fiber passes in the mantle connective (m.c.) to the stellate ganglion (st.g). Here it ends but makes contact with a whole set of third-order giant fibers (g.c.3) which activate the muscles of the mantle, making the jet (from Young, 1939).

To answer this we must look more carefully at what we mean when we say that the nervous system serves for communication. We are using words borrowed from human activities in which a sender has a message calling for some action that he expects from a recipient. He passes signals in what we call a code along a channel to the receiver, who decodes it and selects the required action from the repertoire, or set, of programs available. There are very many fascinating things we could say about this situation. For the present, notice firstly that the activity of communication presupposes an aim or purpose that is to be achieved by choosing the right program from a set. Further it makes use of some arbitrary code of signals, preset by past history and "understood" by transmitter and receiver. Living things are the only systems that we know of that maintain themselves by communication in this way. So what we are doing is to use the words that have been developed to describe human social life to describe all living things. For the present we are concentrating on nervous messages themselves, and we notice that the analogy suggests that they be called signals in a code. Physiologists are beginning to talk about nerve impulses in this way but curiously enough the physiologists who win Nobel Prizes for the study of nerve fibers seldom, or never, use words such as "code" or "symbol." They stick to the dear old terms "nerve impulse" and "action potential." They have indeed been able to find out a very great deal about the physical changes that are involved in the transmission of the nerve message, without thinking much about what the message communicates. To be unkind one might say it was like giving a Nobel Prize for Literature to people who had advanced knowledge of typewriters, or of ink, or perhaps of radio transmission! I may say that many of my best friends are Nobel Prize winners—at least they have been until now!

But there are two further turns of the screw that physiologists must suffer. The significance of signals in a code is that they symbolize the matters to be communicated. If we are to describe the effects of our nerve impulses properly, in this analogy we must say that they are significant because they are

symbols, that is, they stand for or represent either some event in the outside world or some inner need or some action to be performed at the decoding end of a communication channel. We say that a sign or a signal becomes a symbol or representation for something else when it has the effect upon us of that something. A traditional picture of a horse symbolizes horse for us; but the horse in Picasso's "Guernica" does more, it symbolizes also fear and horror.

I claim, therefore, that we shall learn to understand better how the nervous system works if we consider how the operations of each part of it represent or symbolize either some change in the inner or outside world or some instruction for action, passing outward from the brain to the muscles or glands. Let us then see what the various parts of the nervous system in our cephalopods serve to symbolize.

SYMBOLS FOR GRAVITY AND MOVEMENT

Cephalopods, like other animals, arrange their behavior in such a way as to respect the demands of gravity. To be able to do this they have within themselves parts which by their physical structure symbolize gravity and movement. These are, as it were, little models of those features of the universe. Cephalopod statocysts are based on principles surprisingly similar to those used by vertebrates, including man (fig. 6). Like our own inner ear, they combine receptors for maintaining orientation with respect to gravity with others that are sensitive to the angular accelerations due to movement of the animals.

The gravity receptors illustrate well the principles involved in symbolization. To meet the task of correct orientation in relation to the earth's surface, there is present in the statocyst a little model to represent gravity, a stone hanging upon sensory hairs. These hairs send streams of action potentials whose pattern thus symbolizes the position of the animal in relation to gravity. The connections of these nerve fibers must be meticulously arranged to ensure that the various muscles pull to pre-
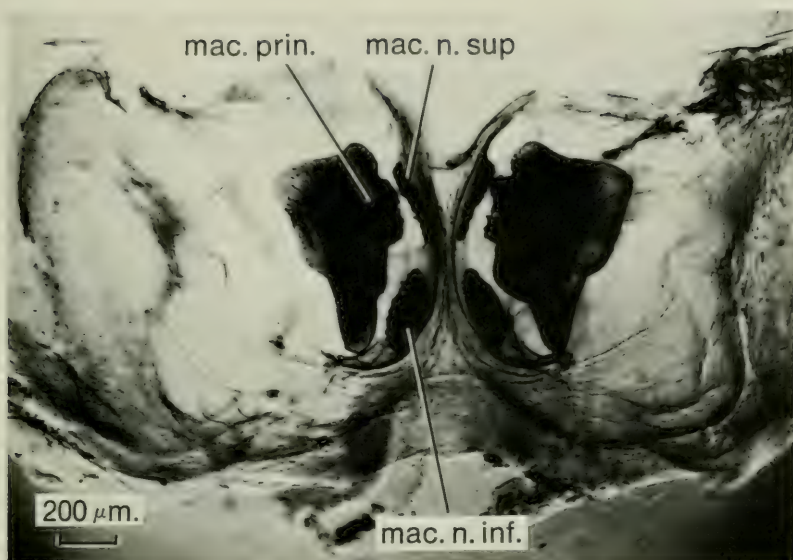
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FIG. 6. The statocyst of the squid *Loligo*, as seen from in front. The calcium salts in the statoliths (the gravity stones) make them opaque. There is one very large one on each side, composed of crystals of aragonite. This stone lies in the transverse plane attached to sensory hairs of the macula princeps (mac. prin.). There are two other patches of sensory cells, carrying numerous small crystals. The macula neglecta superior (mac. n. sup.) lies nearly in the sagittal plane, the macula neglecta inferior (mac. n. inf.) in an oblique horizontal plane.

cisely the correct extent to hold the animal upright (fig. 7). If the statocysts are destroyed this is no longer possible. Notice, then, that the model serves to allow the action system of the animal to maintain its proper relation with the rest of the world— the essential feature of living.

For the detection of angular accelerations the cephalopods have ridges of sensory hairs, the cristae, carrying very light flaps, the cupulae. The cristae run along the sides of the stato- cyst sac in four directions, at right angles to each other (fig. 8). When the animal turns, the displacement of the wall relative to the fluid contents of the statocyst moves the cupula of one or more of the ridges according to the direction of movement. The signals set up by the hair cells of the crista thus represent the

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FIG. 7. Drawings by M.T. Wells to show how pupil of a normal octopus is always held horizontal (a-e). In f and g, are shown the positions of the pupils in an animal from which both statocysts had been removed.

animal's own movements. By their connections these nerve fibers then initiate compensatory movements, especially of the eye muscles.

This system is obviously similar to that of our own semicircular canals. It is indeed striking that in the more active cephalopods, such as the squids, the statocyst has become divided up and curved into shapes that in effect constitute actual canals. Our three semicircular canals serve to represent angular accelerations in three planes of space. What are the squids doing with *four* cristae? It may be that the answer is that with the fourth they detect linear acceleration forward or backward. These animals can move readily in these two directions, which is a feat not easily achieved even by their rivals the fishes. Budelmann (1975) has shown that the cristae are indeed capable of responding to linear acceleration (unlike the semicircular canals).
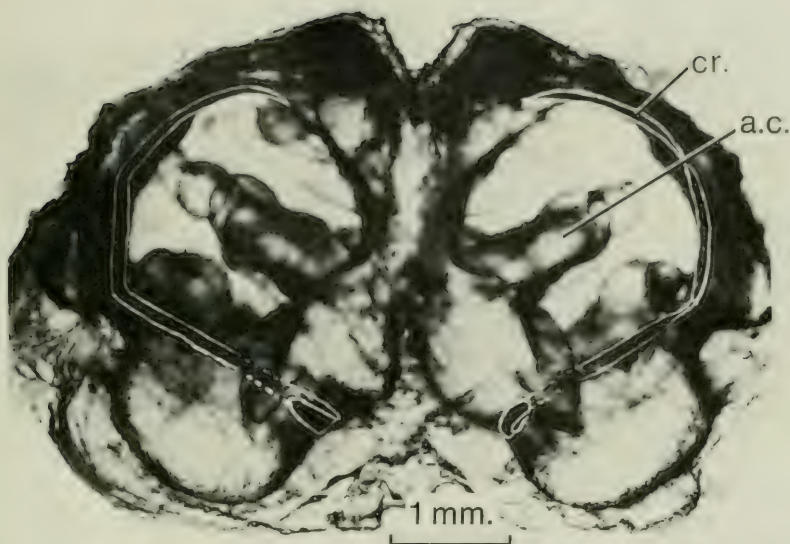
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FIG. 8. Statocyst of the fast-moving squid *Loligo*, seen from above. The stato-liths shown in figure 6 have been removed. The white outlines show the course of the crista (ridge) of sensory cells (cr) mainly for detecting angular accelerations. The ridge runs (on each side) across in front, along the side, across the back and then up in the vertical plane. The cavity has curved sides and is divided up by a number of projections (a.c.=anticristae). The effect is a restriction of fluid movement similar to that accomplished by the semicircular canals in vertebrates.

It is interesting to note that in octopuses and other cephalo-pods that do not make rapid turning movements the whole system is changed. The sac is very large and the anticristae are reduced or absent, leaving a single volume of fluid whose inertia gives greater sensitivity to slow movements (fig. 9). So in every animal the structure and connections of the sense organs have come to represent the environment in which it lives. Notice that the model that the animal contains represents not only the features of the world but also the actions that the animal must itself perform to keep alive. The models in the brain are not static pictures, they are the written plans and programs for action. In squids the giant cells that produce the jet lie very close indeed to the statocyst. If the animal is suddenly disturbed it immediately produces a jet. This plan of action does not have to
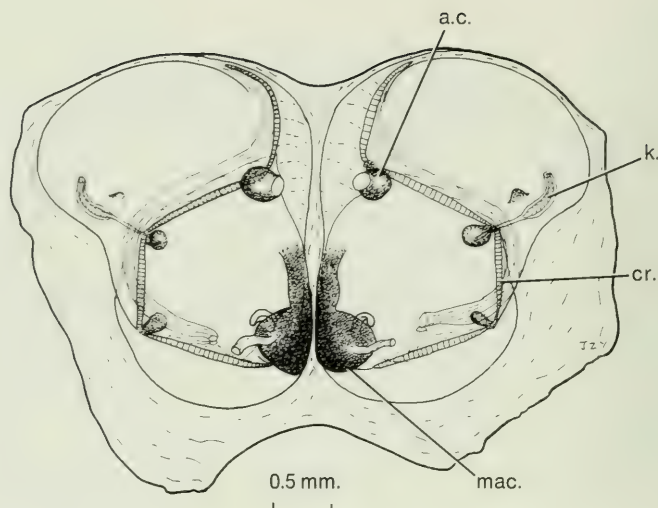
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FIG. 9. The statocyst of the slow-moving squid *Taonius*, seen from above. The macula (mac.) and its stones are quite different from those of *Loligo*. The sac is large and the anticristae (a.c.) are small and few, so that the cavity is not divided up into "canals." K. is Kölliker's canal, a blind ciliated tube of unknown function; cr = crista.

be learned. It is written into the inherited wiring pattern.

In man and other vertebrates the cerebellum is a very important part of the system for control of movement. We have recently realized that there are lobes in the brains of cephalopods that contain large numbers of very small parallel fibers, strikingly like those of our own cerebellum (figs. 10, 11). We do not yet understand the full significance of these arrangements but a possible explanation is that the fine fibers serve to represent *time* (Braitenberg, 1967). They conduct very slowly and this may determine the braking action that terminates a movement. Many actions of the muscles are *ballistic*, in the sense that the ending of their contraction is determined when it begins and not by any feedback en route.

In ourselves the ear has the further function of detecting sound. Cephalopods seem to have no capacity for responding to vibrations, except those of very low frequency. This is very strange since water transmits vibrations that could have very
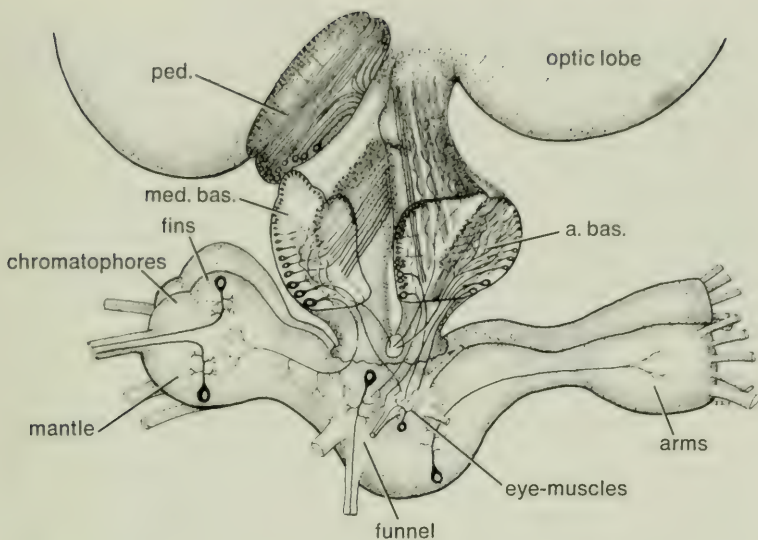
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FIG. 10. A diagram of the brain of a squid showing the four sets of fine parallel fibers, somewhat similar to those in the vertebrate cerebellum. The suboesophageal lobes lie below and control the various movements as shown. The cerebellum-like lobes lie above them and are called the anterior basal (a.bas.), median basal (med. bas.) and peduncle lobes (ped.). The parallel fibers run in different planes; two sets are in the anterior basal lobe, one in each of the others. Notice that these lobes send fibers to the lower motor centers.

great symbolic value and indeed the fishes, great rivals of the cephalopods for domination of the waters, hear very well.

LEARNING SYMBOLIC VALUES

All the behavioral responses we have considered so far have been the consequence of connections laid down during development, but cephalopods are provided also with considerable powers of learning. Far less of course than in mammals or man but still enough to provide us with much information about the processes that are involved in memory formation. It is here that it becomes especially important to pay attention to our conceptual framework and language. The essence of learning is the attaching of symbolic value to signs from the outside world. Images on the retina are not eatable or dangerous. What the eye

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FIG. 11. Section of the peduncle lobe of a squid showing the fine parallel fibers. Stained by the Golgi method, which picks out a few fibers. The photograph has been retouched.

can provide is a tool by which, aided by a memory, the animal can learn the symbolic significance of events. The record of its past experiences then constitutes a program of behavior appropriate for the future.

Octopuses have two separate memory systems. One allows them to make appropriate responses to things that they see; the other does the same for the tactile and chemical properties of objects touched by the arms (fig. 12). These systems lie at the top of the hierarchy of nerve centers in the sense that they make the decisions as to which movements shall be executed by the lower parts. To revert to our military metaphor, they are the General Staff. They receive intelligence from the outside world and then write plans for programs of action by the whole army, in the light of their memory records of past experience.

With the visual system an octopus can learn to make attacks at one shape but to retreat from another. With the touch system
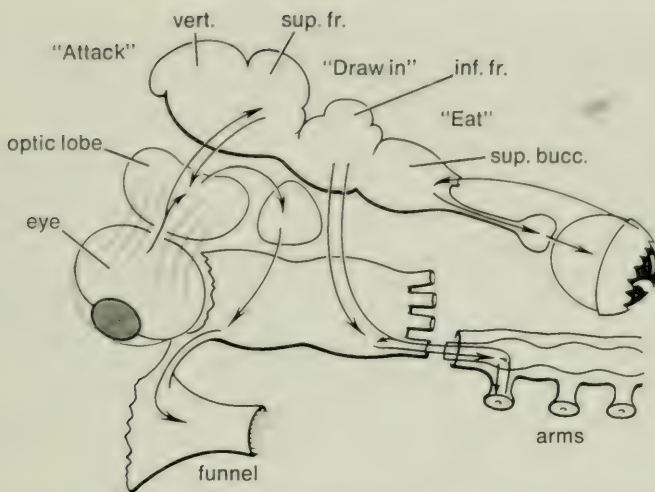
FIG. 12. Diagram of the brain of an octopus showing the parts that make up the two memory systems. The two are outgrowths from the superior buccal lobe, which controls the eating system (sup. bucc.). The inferior frontal system (inf. fr.) receives information from the arms and provides a memory regulating which objects are drawn in. The superior frontal (sup. fr.) and vertical (vert.) lobes are part of the visual memory, serving to decide which objects should be attacked for food.

he can learn to discriminate degrees of roughness and also chemical differences, detected by the suckers (Wells and Wells, 1956; Wells, 1963) (fig. 13).

The visual system has features again surprisingly like those of vertebrates in their principles of operation, in spite of great differences in detailed anatomy. We can see from these principles the stages that are necessary for the learning of symbolic significances by vision or touch.

FEATURE DETECTORS

The first essential is to have sensors that are competent to extract relevant information from the world. We know little about the physiology of these in cephalopods but something of their anatomy. There are cells with receptive fields in the outer parts of the optic lobes that seem suited to detect contours, as
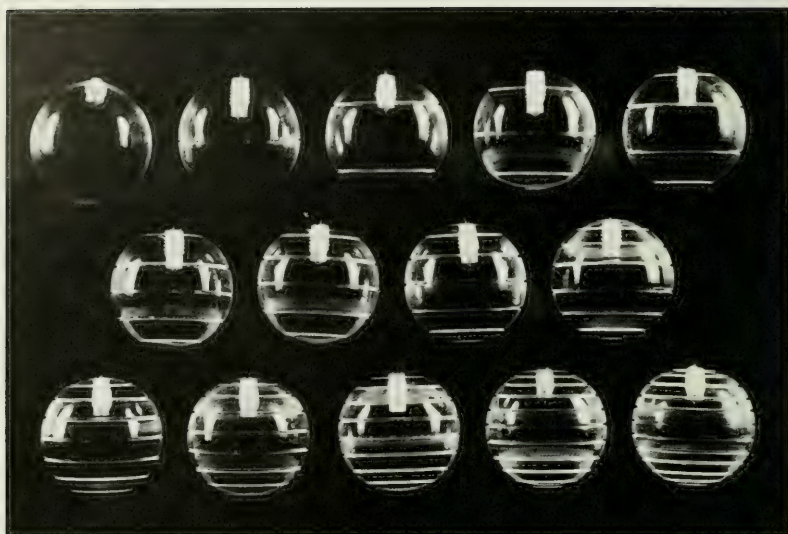
FIG. 13. Series of plastic spheres used for training octopuses to distinguish various degrees of roughness.

do cells of the visual cortex of mammals (fig. 14). Octopuses can be trained to react differentially to rectangles with vertical and horizontal orientations. It is probable that these features are detected by the receptive fields of these second-order visual cells, which seem to be tuned to receive signals from rows of optic nerve fibers. We note that such a system depends on a detailed somatotopic projection from the sensory surface of the eye. This presents a literal map of outside events, from which the brain then records certain features as it writes the programs that will determine its future actions. Moreover, these feature detectors lie in a layered system of neuronal processes, the plexiform layer, which is surprisingly like the layered structure of the vertebrate retina (fig. 15). Contributing to this layered neuropil are great numbers of amacrine and horizontal cells, with processes limited to the plexiform layer. Some extend over long distances, others are quite short, and we have as yet no information as to how any of them operate. Their presence, however, in essentially the same relations in cephalopods and
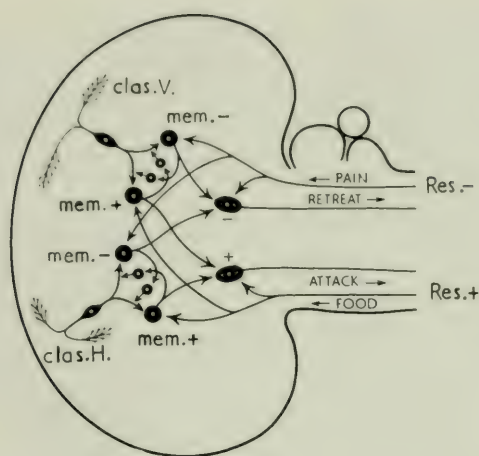
FIG. 14. Diagram of the optic lobe of an octopus to show the system by which it is suggested that visual contours are detected and memory records made that will control future behavior. Clas. V. and clas. H. are the "classifying cells," which respond to particular visual features (e.g., vertical or horizontal rectangles). The octopus can be trained to attack or avoid either of these, so the pathways from them msut lead to motor systems for attack and retreat. Following an attack the animal will receive either food or pain. The suggestion is that signals from the lips (food) or from the body (pain), besides promoting attack or retreat, will activate the small cells, which produce an inhibitory transmitter and block the unwanted pathway, leading to greater use of that which is "correct." The memory cells (mem.) only discharge if they receive signals both from the classifying cells and from the indicators of results (Res.+ and Res.-). The system is shown biased as it would be if the horizontal rectangle had been given food and the vertical shocks.

vertebrates should surely help us to find the principles that are involved in the extraction of significant visual features. Pribram (1971) has suggested that such systems recall the logical organizations necessary for encoding by and/or gates. We can also surmise from the work of Dowling and Werblin (1969) on the retina of the mud-puppy (*Necturus*) that these elaborate networks operate essentially as analogue computers, using patterns of graded electrical signals to compute from the patterns that are sent to them from the retinal receptors suitable all-or-none signals to pass on to the next stage in the brain.

Unfortunately, we know rather little about how to pursue such signals, either in cephalopods or vertebrates, to the points
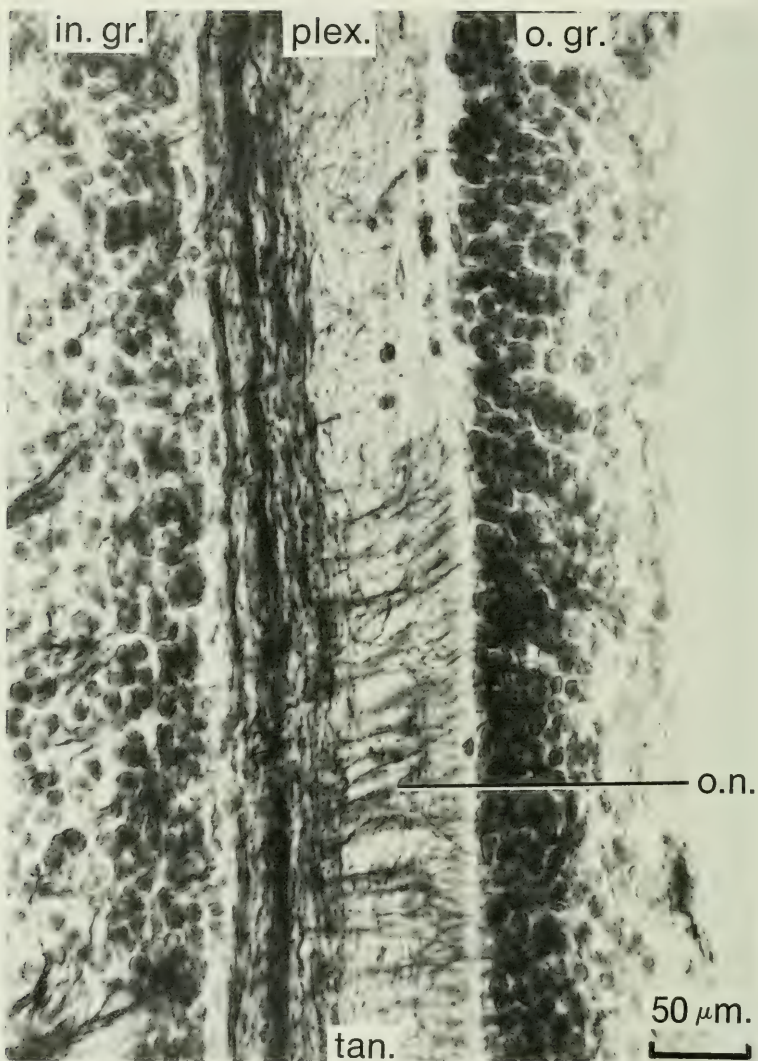
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FIG. 15. Photograph of a section of the surface of the optic lobe of an octopus, showing how it resembles the vertebrate retina. There are outer and inner granule cell layers (o. gr. and in. gr.), with a plexiform layer between (plex.). The optic nerve fibers come in from the right (o.n.). They have disappeared from the upper part of the figure where some of them had been cut some days previously. The inner tangential bands of fibers in the plexiform zone (tan.) are the receiving dendrites of the "classifying cells" shown in figure 14. They have remained intact. Cajal's silver stain.

at which the changes occur that constitute the writing of a new action program by the memory mechanism. In squids we can say that there are only one or two further synapses between the feature detectors and the giant cells. Therefore, although the optic lobes are indeed large and complex, there is no need to suppose that any very elaborate system of operations has to intervene between detection and behavior, even in learned behavior.

However, somewhere in this pathway there must be the possibility of an alteration in connection patterns, if that is the mechanism by which the memory system works. I have suggested that this is done by the operation of a switch system that reduces the probability of using one pathway in favor of the other (fig. 14). It may be that once one path begins to be used rather than the other there will also be a subsequent increase in its availability, perhaps by added synaptic connections or efficacy, as has been suggested, following Cajal (1895, see 1953 p. 887), by many workers (e.g., Hebb, 1949; Young, 1950). But whatever mechanism is used to establish the symbolic value of some set of nervous signals, it must involve a *reduction* of the number of possible behavioral responses. The octopus can originally react either positively or negatively to a horizontal rectangle; his experience restricts him to only one of these responses. A given signal cannot symbolize *both* something good and bad. I have suggested that the switching of each single neuronal pathway constitutes a unit of memory or mnemon. It is the single "word" of the writing that constitutes the new program of action. The octopus is a very simple creature and perhaps it learns only single words. We have to learn not only words but whole "sentences," indeed whole "books," which constitute the action programs that become written in our memories.

For the establishment of symbolic value it is essential that the results of action can be referred to a standard, which must ultimately be set by the genetic composition, the historical information encoded in the DNA. Such signals of the results of action come from the taste systems on the one hand and the

pain systems, producing aversive responses, on the other. We do not know much about them in octopuses but there is evidence that if they are prevented from reaching to the appropriate parts of the brain no learning is possible. We notice that these nerve impulses, like all others, are symbolic, in this case symbolizing internal states that are either satisfactory or unsatisfactory for life. The symbolic value is established by the long sequence of selections that have produced appropriate DNA. Those organisms that do not have an appropriate taste for food and life or skill in avoiding pain do not survive.

The anatomy suggests that in the octopus, as in vertebrates, special patterns of connection are used to allow these reference signals to meet with those coming from the outside world. In both the visual and touch memory systems of the octopus there are lobes in which this interaction can take place (fig. 16). The
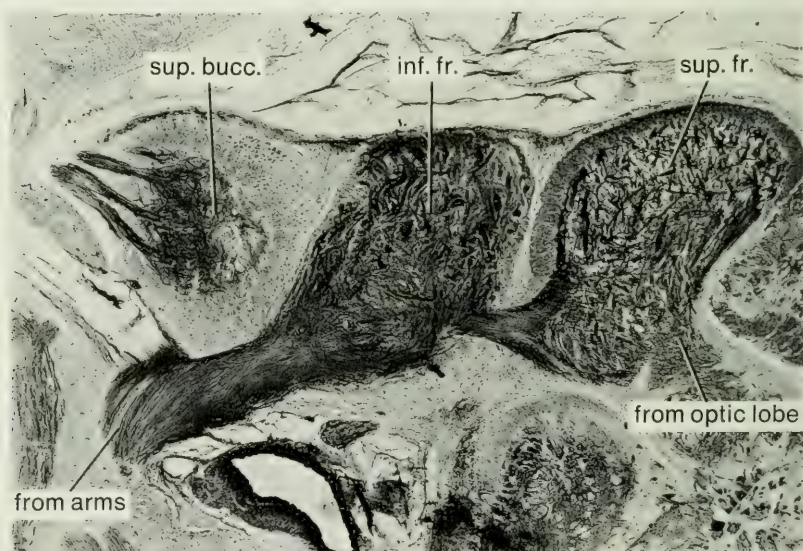

FIG. 16. Photograph of sagittal section through the front part of the brain of an octopus, showing the inferior frontal (inf. fr.), superior frontal (sup. fr.) lobes, and superior buccal lobe (sup. bucc.). These serve to mix signals of taste (from the lips) with those from the arms and optic lobes (respectively). The two lobes have similar structures, with many interweaving bundles, allowing for the mixing. Cajal's silver stain.

output of the lobes in both cases passes through a further lobe consisting of large numbers of very small cells, the vertical or subfrontal lobes (fig. 17). Many lines of investigation have shown that these lobes are involved in the process of recording in the memory, but are not absolutely essential for it. Their action seems to be particularly in restraining the animals from performing actions that are likely to be damaging. The numerous minute cells in these lobes can be seen with the electron microscope to be packed with synaptic vesicles (fig. 18). How they operate remains a very interesting question.

In general we can say that if learning consists in increasing the probability of performing certain "correct" actions when symbols appear, then it is necessary to have inhibitory systems to restrain the performance of other actions. A multichannel system such as this operates by means of a maximum amplitude filter in which many elements may be active but only the *most* active takes control (Taylor, 1964). It is suggested that the cerebral cortex contains systems that act in this way. Perhaps the prefrontal lobes in particular have a restraining influence in
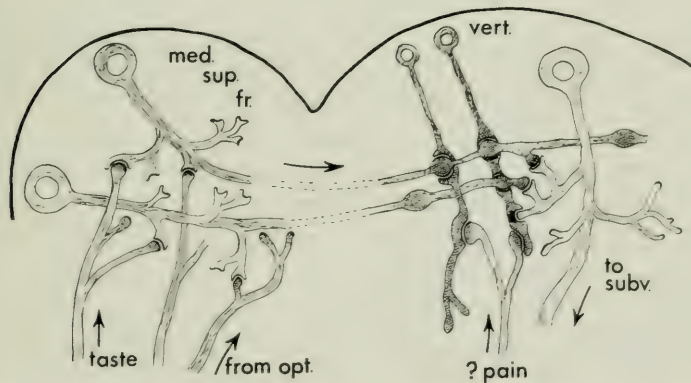

FIG. 17. Diagram of some connections of the median superior frontal (med. sup. fr.) and vertical lobes (vert.) of an octopus as shown by electronmicroscopy. The short amacrine cells in the vertical lobes are packed with synaptic vesicles. They are influenced by the fibers from the superior frontal and also by those entering from below and probably signalling pain. They influence larger cells leading to the subvertical lobe (subv.) and so back to the optic lobes (opt.).
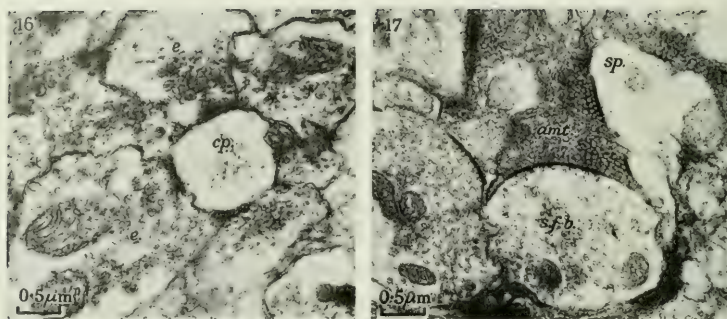
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FIG. 18. Electronmicrographs of synaptic contents in the superior frontal (on right) and vertical (left) lobes of an octopus. The synapses in the former are between incoming fibers (e) and cell processes (cp.). In the vertical lobe the amacrine trunks (amt.) receive synapses from the axons of the superior frontal (s.f.b.) and transmit to spines (sp.) of cells that carry signals away from the lobe.

man, allowing the performance of such delicately graded actions as those of effective speech in a social context.

Human brains, like those of octopuses, must contain reference systems to determine which lines of action are likely to be successful in maintaining life. We can indeed begin to see some evidence that they operate in ways rather like those described. Ungerstedt (1971) and others have shown that there are systems of aminergic pathways leading upward from centers in the medulla to the hypothalamus and on to the limbic system and frontal cortex (fig. 19). These pathways, such as that beginning in the nucleus coeruleus, come from regions where fibers from the taste buds enter the brain. Crow and his colleagues have produced evidence that rats with lesions to this pathway cannot learn to run a maze for food reward (Anlezark, Crow, and Greenaway, 1973). Moreover, with electrodes implanted in these regions animals will press repeatedly for self-stimulation. There are controversies about these experiments, but it seems very probable that we are approaching here close to the core of many problems that have worried mankind for centuries, and do so still. The reference signals that come from these pathways, and from the hypothalamus, provide the aims and objectives of our lives and the course of our learning. Of course crude
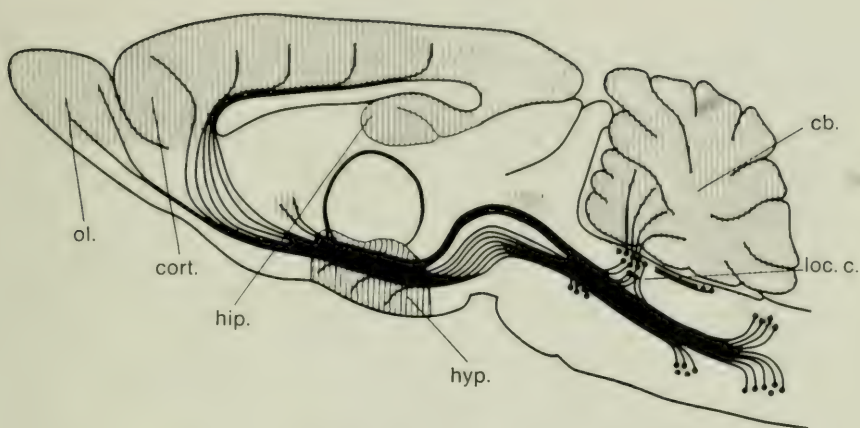
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FIG. 19. Diagram of the ascending pathways on the rat's brain that use the transmitter noradrenaline. They begin in the locus coeruleus (loc. c.) and other centers in the hind brain. From here they ascend to the cerebellum (cb.), hypothalamus (hyp.) and finally reach to the cerebral cortex (cort.), olfactory bulb (ol.) and hippocampus (hip.). The terminal areas are shaded (after Ungerstedt, 1971).

rewards do not necessarily enter into every associational act, especially in man. We have acquired more subtle systems of reward to supplement those of taste and pain. Nevertheless, we begin to see how life depends upon symbolic signs of life values, which are used to give symbolic significance to the signals we receive from the outside world.

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AN EVOLUTIONARY INTERPRETATION
OF THE
PHENOMENON OF NEUROSECRETION

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AN EVOLUTIONARY INTERPRETATION
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FORTY-SEVENTH
JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN

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*Berta Scharrer, *An Evolutionary Interpretation of the Phenomenon of Neurosecretion*; April 12, 1977

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AN EVOLUTIONARY
INTERPRETATION OF THE
PHENOMENON OF NEUROSECRETION

INTRODUCTION

Almost 50 years ago, Ernst Scharrer (1928) made a discovery that was received by the scientific community with great skepticism, if not with outright rejection. It marked the beginning of a scientific adventure that has given rise to one of the most challenging pursuits in neurobiological research, the results of which have been dramatic. Based on cytological observations in a teleost fish, *Phoxinus laevis*, he postulated that certain groups of distinctive cells in the hypothalamus ("neurosecretory neurons") engage in secretory activity to a degree comparable to that of endocrine gland cells. He further suggested that this activity may be related to hypophysial function.

A search in the literature yielded but one comparable report calling attention to the occurrence of "glandlike" nerve cells in another part of the central nervous system, the spinal cord of skates (Speidel, 1919). Subsequent studies demonstrated the almost ubiquitous occurrence of such neurons throughout the animal kingdom. Yet, for many years to come, the spotlight remained on the hypothalamic neurosecretory centers of the vertebrate series. The elucidation of their close affiliation with the pituitary gland eventually gave rise to a new discipline, neuroendocrinology.

However, recognition of these unusual neural elements represents a challenge to the neuron doctrine, according to which nerve cells are most commonly thought of as being designed for the reception of stimuli, the generation and propagation of bioelectrical potentials, and the rapid, synaptic transmission of signals to contiguous recipient cells. "Conventional" neurons make only very restricted use of chemical mediators in the form of special neurotransmitters and certain other regulatory substances.

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In contrast, the primary activity of the classical neurosecretory cell consists of the manufacture of a distinctive (proteinaceous) product in sufficient quantity to function in a hormonal capacity. Furthermore, its axon terminates, without establishing synaptic contact, in close proximity to the vascular system. No wonder that, because of these "aberrant" attributes, neurosecretory phenomena were long looked at askance and frequently brushed off as signs of degenerative or postmortem changes. Today, this mistrust no longer exists, as will become apparent in the following discussion.

An important step forward was the demonstration that the "posterior lobe hormones," e.g., vasopressin, are derived from peptidergic neurosecretory nuclei of the hypothalamus and are transported by axoplasmic flow to the posterior pituitary where they are released into the general circulation (Bargmann and Scharrer, 1951). At last, the endocrine nature of some of these neuroglandular elements had been established.

But even then a vexing question remained. Why should the body make use of nerve cells to provide hormonal messengers in order to reach terminal effector sites such as the kidney? This conceptual difficulty stems from the established custom of classifying neuroregulatory and glandular functions as two distinctly separate categories. In reality, there are cogent reasons for bridging this gap, based largely on evidence that is implicit in the evolutionary history of integrative systems.

PHYLOGENY OF NEURAL SYSTEMS OF COMMUNICATION

A careful consideration of the phylogenetic, and to some extent the ontogenetic, development of such informational systems has made it increasingly clear that the manufacture and release of secretory products is an old and fundamental attribute of neuronal elements. The evolutionary approach, featured in this article, is based on the premise that the most elementary integrative mechanisms existing today may resemble those of our remote ancestors (Pavans de Ceccatty, 1974).

By reason of its phylogenetic derivation from a pluripotential epithelial element, the primitive nerve cell can be viewed as a

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functionally versatile structure, endowed with the capacity to dispatch both long distance and localized chemical signals. This concept is supported by a substantial body of information on neuroregulatory mechanisms encompassing all multicellular animals (see Lentz, 1968; Highnam and Hill, 1977). Starting with the simplest forms among them, we find in sponges a reticular neuroid tissue complex whose components do not yet satisfy all the criteria of nerve cells. The first primitive neurons with elementary synaptic contacts appear in the lowest eumetazoans, the coelenterates.

What seems important in the context of the present analysis is that in both groups some of the cells mentioned display cytological signs of neurosecretory activity. The cytoplasmic granules observed here are comparable to those of higher animals in that they stain with alcian blue and, in electron micrographs, appear electron dense and membrane-bounded with diameters of 1,000-1,700 Å (Pavans de Ceccatty, 1966; Lentz, 1968; Davis, 1974). Neurosecretory granules are abundant in the nervous system of planarians. In the ganglia of annelids more than one-half of all neurons are of the neurosecretory type.

Even more relevant is the fact that distinctive hormonal functions as well as other "nonconventional" neuroregulatory roles can be ascribed to the neurosecretory neurons of these lower invertebrates. Tests with isolated neurosecretory granules of the coelenterate *Hydra* reveal that their content regulates growth and differentiation, especially during regeneration (Lentz, 1968). This neuromediator also seems to participate in the induction of gametogenesis and sexual differentiation (Burnett and Diehl, 1964). Similarly, neurosecretory control, over a distance, of growth during development and regeneration and of certain reproductive events has been demonstrated in planarians (Lentz, 1968; Grasso and Benazzi, 1973) and in annelids (Hauenschild, 1974).

The salient point is that in none of these primitive invertebrates have "regular," i.e., nonneural glands of internal secretion been identified. Therefore, at this level of differentiation, the nervous system seems to be the only agency available for carrying out all of the existing endocrine functions. Neurohormones thus hold the

rank of the phylogenetically oldest integrative long-distance messengers, and the endocrine type of coordination accounts for a relatively large sector of neuronal activities in lower invertebrates. In other words, far from being a latecomer and a rare exception, the neurosecretory neuron dates back to the very beginning of the development of neural structures. Furthermore, its versatility indicates that it has remained closer to the nerve cell precursor than has the more specialized "conventional" neuron.

In the course of evolution the scene shifts in more than one direction. Not only is there a staggering increase in the number of neurons, as primitive nervous systems give way to more and more elaborate structures but, in the most advanced forms, the vast majority of "conventional" nerve cells engage in interneuronal synaptic transmission involving the release of tiny, precisely metered amounts of chemical transmitter substances. Some of these special messengers are used over and over again. Therefore, in these billions of neurons, the demands for secretory activity have become greatly reduced.

Another, equally important, evolutionary change in design is the evolvement of extraneuronal hormone sources. The structural and functional attributes of the endocrine apparatus have long been thought to be as clearly defined as have those of neurons. Yet, the dividing line is by no means complete, on account of the neuroectodermal origin of peptide-producing endocrine cells to be discussed below. According to this concept (Pearse, 1976), the relationship between the neuronal and nonneuronal hormone sources of the hypothalamic-hypophysial complex is even closer than formerly recognized, since both share their origin from the same precursor cells in the ventral neural ridge. However, in spite of this embryonic background, the cells of the adenohypophysis should not be classified as neural elements. They have crossed over to join the ranks of the endocrine system. This process of metamorphosis entails the loss of structural and cytochemical neural attributes and the acquisition of endocrine qualities which these polypeptide-hormone-secreting cells share with the rest of the endocrine apparatus.

The evolvement of this second integrative system that specializes in hormonal communication, making use of various types of

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chemical messengers, argues against the need for blood-borne neurochemical mediators in higher animals. Quite obviously, its existence should relieve neurons from doing double duty.

NEUROENDOCRINE INTERACTIONS

In reality neurohormones do not become obsolete after the acquisition, by arthropods and vertebrates, of an endocrine apparatus proper. Instead they take over a novel and highly significant role, that of mediation between the two systems of integration. As has been pointed out repeatedly in the past (Scharrer, 1970-1974), the neurosecretory neuron, having retained its dual capacity, is ideally suited and programmed for this special task.

In view of this shift in functional significance, the question raised earlier, concerning the raison d'être of first-order neurohormonal mechanisms even in the most highly developed organisms, now appears in a different light. Such one-step systems, e.g., the control of water metabolism by vasopressin, have certainly become overshadowed by those constituting the all-important neuroendocrine channel of communication. They do not even seem to be obligatory. Yet, their existence makes sense in an evolutionary perspective, i.e., when interpreted as carryovers from systems operating by necessity in phylogenetically less advanced forms.

NONNEUROHORMONAL PEPTIDERGIC ACTIVITIES

A rather unexpected and challenging result of the detailed ultrastructural analysis of the neuroendocrine axis in vertebrates and invertebrates was the realization that not all the neurosecretory neurons dispatch their messenger substances via the general or the special portal circulation. There are, in fact, several recognized modes of neurochemical communication that are neither strictly neurohumoral (synaptic) nor neurohormonal (blood-borne). One such mechanism is the long known regulation of tissue growth and maintenance, by "neurotrophic substances" (see Smith and Kreutzberg, 1976). The chemistry and extracellular pathway of these diffusible substances released from sensory and motor fibers are still uncertain.

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Information on nonvascular extracellular avenues available to peptidergic neurosecretory messengers is more precise. These variants include the cerebrospinal fluid (see Rodríguez, 1976), zones of extracellular stroma, and even narrow "synaptoid" gaps. Axons laden with neurosecretory material can be observed to penetrate the glandular parenchyma of the adenohypophysis as well as the corpus allatum of insects. In both organs synaptoid release sites occur in close vicinity to, or even in contiguity with, their apparent cells of destination. Furthermore, such spatial relationships are not restricted to endocrine elements, but are also found in a variety of somatic structures, among them various exocrine gland cells and muscle fibers.

Perhaps the most unexpected informational systems are those in which neurosecretory neurons establish synapse-like relationships with other neurons, some of which may themselves be of the nonconventional type (see Scharrer, 1976). The realization that, at least in certain special situations, peptidergic neurosecretory mediators may operate in a manner comparable to that of neurotransmitters has added a new and important facet to the "gestalt" of the classical neurosecretory neuron. The existence of these several intermediary possibilities for the transfer of information by neurosecretory cells has clarified their relationship with the more conventional neuronal types. Consequently, the sharp dividing line originally thought to separate conventional from classical neurosecretory neurons no longer exists. Now the modes of operation of classical neurosecretory neurons actually blend into a continuum of diverse neurochemical activities.

NONCONVENTIONAL INTERNEURONAL COMMUNICATION

What makes the discovery of synaptoid structures between neurons intriguing is that they go hand in hand with increasing physiological evidence in support of the concept that nonconventional (peptidergic) neuroregulators may modulate certain forms of synaptic interneuronal communication. This broader neurotropic activity will undoubtedly turn out to represent a novel and important form of information transfer with far-reaching biomedical implications (see, for example, Constantinidis et al.,

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1974; Sterba, 1974; Brown and Vale, 1975; Plotnikoff et al., 1975; Prange et al., 1975a, 1975b; Vincent and Arnauld, 1975; Brownstein et al., 1976; Guillemin, Ling and Burgus, 1976; Lote et al., 1976).

To cite an example of such known activities among the hypophysiotropic hormones, or factors, TRF (thyrotropin releasing factor) has a modulating effect on synaptic, especially monoaminergic, transmission. Apparently, this role evolved before that of controlling thyrotropin release, and it seems to be of a more general importance (Grimm-Jørgensen, McKelvy and Jackson, 1975; McCann and Moss, 1975; Waziri, 1975; see also Nicoll, 1977). A broader role for the posterior lobe hormone vasopressin, or fragments thereof, is that demonstrated by de Wied and his co-workers (1976) and involved in the control of various forms of behavior. Moreover, effects that differ from conductance changes evoked by conventional neurotransmitters can be elicited in certain neurosecretory neurons of molluscs by the application of vasopressin and related peptides (Barker and Gainer, 1974). Finally, there is new and intriguing evidence that two specific neuronal pentapeptides (enkephalins, Hughes et al., 1975) function as endogenous analgesics presumably by suppressing excitatory synaptic signals implicated in the perception of pain (see Snyder, 1977).

BIOCHEMICAL EVOLUTION OF NEUROSECRETORY MEDIATORS

The evolutionary interpretation of the phenomenon of neurosecretion presented here is not based on morphological and physiological evidence alone. It can be further substantiated by tracing the biochemical history of neurosecretory mediators, even though the picture is still incomplete.

Among the general trends that are beginning to emerge are the following. In contrast to those used in much smaller amounts by conventional nerve cells, the chemical messengers operating in classical neurosecretory neurons of both vertebrates and invertebrates are proteinaceous in nature. Furthermore, the biologically active polypeptides of many neurosecretory neurons are bound by

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noncovalent forces to special carrier proteins, called neurophysins (see Walter, 1975; Watkins, 1975; Acher, 1976b), which are primarily responsible for the selective stainability of neurosecretory material throughout the animal kingdom. Aside from serving as carrier molecules, these proteins may play an active role of their own (Pilgrim, 1974).

Much information is being amassed on the occurrence and precise localization of such neuropeptides and their affiliated neurophysins within the neurosecretory systems of a variety of animals by the use of immunochemical, especially immunoelectron-microscopic methods (see McNeill et al., 1976; Ude, 1976; Zimmerman, 1976). In addition, synthetically produced neurohormones and their analogs are becoming available in increasing numbers. These advances offer valuable tools for the differential determination of the relationships and functional roles of these substances.

There is substantial support for the concept that the characteristic products of presently existing neurosecretory neurons have a common evolutionary origin. Gene duplication, modification, and cleavage of ancestral proteinaceous molecules are presumed to have been involved in the development of chemical entities with more and more diversified functional properties (see Wallis, 1975).

This process seems to be reflected by the fact that enzymatic dissociation is responsible for the biosynthesis of most, if not all, biologically active peptides known today (Tager and Steiner, 1974; Acher, 1976b). For example, the active nonapeptides stored in the mammalian posterior lobe and the corresponding carrier proteins are apparently not synthesized as such in the perikarya of the respective hypothalamic neurons but are cleaved from a precursor of higher molecular weight (Sachs et al., 1969; Gainer, Sarne and Brownstein, 1977). The fact that both components make a strikingly sudden and simultaneous appearance early during fetal development (Pearson, Goodman and Sachs, 1975) supports the view that they share the same macromolecular precursor. Moreover, the impressive structural similarity throughout the entire vertebrate series of neurohypophysial hormones (Heller, 1974; Carraway and Leeman, 1975; Wallis, 1975; Acher, 1976a)

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as well as their corresponding neurophysins (Capra and Walter, 1975; Acher, 1976b; Zimmerman, 1976) suggests that their pres-. ent precursor molecules (prohormones) are derived from closely related ancestral proteins.

The same type of lineage can be claimed for hypophysiotropic factors, the amino acid sequences of which are contained in parent compounds of higher molecular weight. For example, nonapeptides with hormonal activities of their own can play the role of precursor for short-chain principles, such as the tripeptide MIF (MSH-release inhibiting factor, melanostatin), a neurohormone with different functional capacities (Walter, 1974; Reith et al., 1977). Parenthetically, another unexpected feature about nonapeptides is the recently reported presence of vasopressin, unaccompanied by neurophysin, in a cell line from a human lung carcinoma (Pettengill et al., 1977).

Information on analogous proteinaceous compounds in invertebrates is still sporadic. Nevertheless, histochemical and biochemical parallelisms can be recognized. For example, a chromatophorotropin that was chemically identified in crustaceans shows a close resemblance to some of the small hypophysiotropic peptides of mammals (Fernlund and Josefsson, 1972; Carlsen, Christensen and Josefsson, 1976). Furthermore, a chemically synthesized octapeptide was shown to elicit pigment concentration in two types of crustacean chromatophores *in vitro* and *in vivo* (Josefsson, 1975). A similar fully identified neuropeptide is the adipokinetic hormone of insects (Stone et al., 1976). Another case in point is the recent demonstration of immunoreactive TRF (thyrotropin releasing factor) in the ganglia of some gastropods (Grimm-Jørgensen, McKelvy and Jackson, 1975) where, for obvious reasons, its function could resemble only the extrahypothalamic activities demonstrated in vertebrates. An indication of the occurrence of such nonconventional interneuronal communication is the recent observation (Takeuchi, Matsumoto and Mori, 1977) that certain neurons of the snail *Achatina* are differentially affected by fragments of some enzymatically treated nonapeptides, e.g., oxytocin and vasotocin.

Finally, are there common denominators in the biosynthetic and functional features of classical neurosecretory materials and

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of other biologically active peptides produced by neurons and/or glandular elements derived from neuroectodermal precursors (anterior pituitary and other members of the APUD cell series, Pearse, 1976; Pearse and Takor Takor, 1976)?

In underscoring the neuroembryological and cytochemical features shared by these cells, Pearse's intriguing concept clarifies the multiple occurrence, both within and outside the adult nervous system, of a variety of regulatory peptides, including Substance P, enkephalins, endorphins, and several hypophysial hormones. Therefore, all of these peptides may also have in common the mode of their molecular evolution.

An example in support of this proposition is the mounting evidence for the derivation of several such peptides with distinctive physiological properties from a larger parent molecule, the formerly enigmatic pituitary hormone β-lipotropin (Li, 1964). Among its subunits the endorphins (Goldstein, 1976; Guillemin, 1977) are currently receiving much attention because of their analgesic and behavioral effects. The N-terminal of α-endorphin, a short sequence (amino acid residues 61 through 65) apparently representing the analgesically active core, precisely matches that of methionine enkephalin, one of the two specific neuronal pentapeptides already referred to (Cox, Goldstein and Li, 1976; Guillemin, 1977; Guillemin, Ling and Burgus, 1976). Therefore, these endogenous opiates could be generated from the prohormone β-lipotropin, either within the brain or in the pituitary, in which case they could reach their sites of action via the circulation or the cerebrospinal fluid (Reith et al., 1977).

There are also several indications of functional parallelisms. One is the demonstration that, in company with several hypophysiotropic polypeptides, enkephalin and endorphin (Dupont et al., 1977; Simantov and Snyder, 1977) as well as Substance P (Kato et al., 1976) elicit the release of growth hormone, ACTH, FSH, and prolactin. Another is that Substance P, like enkephalin, endorphin, and several hypophysiotropins, may act as a modulator of neuronal activity (see Zetler, 1976).

Neither enkephalins nor opiate receptors have thus far been found among invertebrates (Snyder, 1977). Nevertheless, the features that all the biologically active peptides known to date have

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in common add up to the following generalization. In the course of a long evolutionary history, ancestral macromolecular proteins have given rise to a variety of related compounds. Multiple sites of cleavage and molecular modulation seem to have resulted in the acquisition and dissociation of diverse, e.g., hormonal, neurotransmitter-like, and carrier functions, whereby one active principle may act in more than one capacity. These possibilities, borne out by phylogenetic and ontogenetic considerations, illustrate the principle of biochemical economy.

CONCLUSIONS

An examination of the evolutionary history of neural tissue, and its pluripotentiality in primitive animals, points up its special glandular attributes. The old inherited capacity for secretory activity seems to have been put to use in multiple and specialized ways at consecutive levels of the evolutionary scale. Therefore, the spectrum of available neurochemical mediators and of modes of information transfer that digress from standard synaptic transmission is more diversified than previously assumed, even in higher forms. Hormones derived from neural elements have remained indispensable even after the appearance of the endocrine system proper. The most unorthodox neurosecretory cells giving rise to these blood-borne proteinaceous messengers, as well as those signaling at closer range, have found their place within the range of existing variants. Now that the versatility of the hypothalamic neurosecretory centers and their major role in neuroendocrine integration have been clarified, current interest can turn to extrahypothalamic neuropeptides. This nonconventional minority seems to have a relatively wide distribution within and outside the central nervous system and to function in remarkable ways. Further exploration of the glandular aspects of neuronal function and their relationship with peptide-hormone-producing cells of neuroectodermal origin holds much promise.

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